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A CENTURY OF THE UNITED STATES
PHARMACOPOEIA. 1820-1920

LIQUOR POTASSII ARSENITIS

BY

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INTRODUCTORY STATEMENT

The history of arsenic therapy is of considerable interest in the evolution of the *materia pharmaceutica*. Natural compounds of arsenic, such as realgar and auripigment were used during antiquity,¹ but primarily for external purposes. Because of the change which they produced in the color of copper, arsenical compounds have played an important role during the alchemistic period of chemical history.² As a result, new derivatives of arsenic were discovered,³ some of which at least were destined to play a role in the battles between the iatrochemists and the representatives of the old or Galenical School of Medicine.⁴ A larger increase to the number of arsenic compounds, however, did not come until the close of the eighteenth and the beginning of the nineteenth cen-

¹ For a concise statement of the knowledge of the ancients, see Kopp, *Geschichte der Chemie*, vol. 4, p. 89.

Berendes, *Des Pedanios Dioskurides Arzneimittellehre*, p. 531 (Chap. 120 : Arsenikon; and Chap. 121: Sandaracha.)

Pliny, *Natural History* (Bohn's Classical Library, vol. 6, p. 104 (Orpiment) and p. 220 (Sandarach and Arrhenicum).

Scribonius Largus (Felix Rinne, *Das Rezeptbuch des Scribonius Largus*, vol. 5 of R. Kobert, *Historische Studien aus dem Pharmakologischen Institute der k. Universität Dorpat*, p. 79 (Auripigmentum) and p. 84 (Sandaraca.)

For a more detailed account see, "Historical Notes on Arsenic and its principal combinations: by G. F. Babcock, *New Remedies*, vol. 12, (1883) pp. 98, 131 and 170.

² Comp. El. v. Meyer, *History of Chemistry* (3rd ed.) p. 58: "On account of this behaviour, the pseudo-Geber calls arsenic *Medicina Venerem dealbens*". See also Kopp, *Geschichte der Chemie*, vol. 4, p. 94.

³ The *arsenicum album* (As₂ O₃) of the alchemists; the *arsenicum fluum* of Paracelsus (arsenic acid or its potassium salt). Kopp, *Geschichte der Chemie*, vol. 4, p. 95.

⁴ Meyer, *History of Chemistry* (2d ed.) p. 94.

ture.⁵ Still later followed the organic derivatives of arsenic that formed the basis of the classical researches by Bunsen.⁶ Comparatively few of these have found application in medicine, one of the latest being the much discussed specific "606" or *salvarsan*.⁷

If the chemotherapy of arsenic includes but few of its compounds, pharmacopoeial preparations of the derivatives of this element are even less numerous. Those of the U. S. P. and N. F. are but seven in number and can be grouped as follows:

- 1.) Solutions of arsenous acid and its salts:
 - 1.) *Liquor Acidi Arsenosi*, U. S. P.
 - 2.) *Liquor Potassii Arsenitis*, U. S. P.
- 2.) Solutions of arsenates:
 - 3.) *Liquor Sodii Arsenatis*, U. S. P.
 - 4.) *Liquor Sodii Arsenatis*, Pearson, N. F.
 - 5.) *Liquor Arsenicalis*, Clemen's, N. F.
- 3.) Solutions of arsenic trihalides (or rather "double salts") :
 - 6.) *Liquor Arseni et Hydrargyri Iodidi*, U. S. P.
 - 7.) *Liquor Auri et Arseni Bromidi*, N. F.

I. SOLUTIONS OF ARSENOUS ACID AND ITS SALTS.

The so-called "arsenious acid" of the older chemists, our arsenous acid anhydride, or arsenic trioxide, is but sparingly soluble in water, yet sufficiently soluble to form solutions with a 1 p. c. As_2O_3 content. Nevertheless such a solution is not official in any of the latest editions of the pharmacopoeias.⁸ Neither does the simple solution appear to be prescribed at present by physicians, although arsenic trioxide is frequently prescribed in solid form as pill,⁹

⁵ Kopp Geschichte der Chemie, 4, p. 96.

⁶ The reprint of these has been edited by A. v. Baeyer in Ostwald's Klassiker der exakten Wissenschaften, vol. 27.

⁷ This epoch making discovery is discussed by Schweizer "Ehrlich's Chemotherapy—a new science" in Science, vol. 32, p. 809. (Dec. 9, 1910.)

⁸ In the French Codex of 1884 a *Soluté Arsenical ou Minéral* (Boudin), one-tenth as strong as the corresponding U. S. P. arsenical solution, was official, but has been dropped in the latest edition. See also Dorvault, L'Officine, 15th edition (1910), p. 1289, which also gives a formula for a *Soluté Arsenical* (Isnard), which is only one-tenth of the strength of Boudin's solution.

⁹ Arsenic trioxide enters the *Pilulae Ferri, Quininae, Strychninae et Arseni fortiores* of the National Formulary 4th revision; also *Pilulae F. Q. S. et As. mites*, N. F. IV with less arsenic trioxide.

The French Codex of 1866 and 1884, but not the latest edition, contains *Granules d'Acide Arsenique*; also *Pilules Arsénicales* (*Pilules Asiaticques*); see also, L'Officine 15th edition (1910), p. 1061; Binz, Lectures on Pharmacology, vol. 2, (1897), p. 88, translation by Latham.

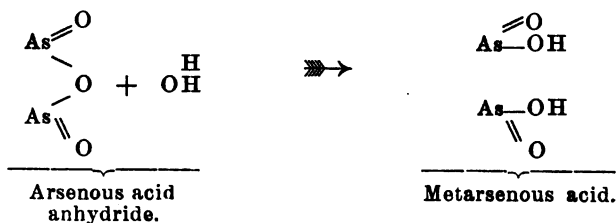
powder,¹⁰ or tablet. The slow solubility of arsenic trioxide in water may be accelerated either by hydrochloric acid or by potassium carbonate. The question may well arise, are these adjuncts mere pharmaceutical conveniences or do the resulting reaction mixtures differ sufficiently chemically to make the products different therapeutic agents? If essentially alike as therapeutic agents, another pharmaceutical question may be asked, viz., are the two solutions required in medical practice to avoid chemical incompatibilities when prescribed with other substances? The first question is answered in the negative by modern pharmacologists.¹¹ The so-called neutral solution being unstable,¹² the acid and alkaline solutions afford pharmaceutical advantages only. Both are official so that incompatibilities may be avoided by using either the one or the other.¹³

In a general way, the chemistry of these two solutions has certain aspects in common, hence may be considered together if for no other reasons than to avoid unnecessary repetition. The reactions involved may be reviewed from the following points of view:

- A.) The hydration of arsenic trioxide.
- B.) The action of an alkali, such as potassium hydroxide or potassium carbonate, on the hydration products.
- C.) The action of hydrogen chloride on the hydration products.

A. Hydration of arsenic trioxide.

When arsenic trioxide, arsenous acid anhydride, is dissolved in water, its hydration to metarsenous and other arsenous acids may be assumed. This hydration finds a ready expression in the following structural formulas of these compounds:¹⁴



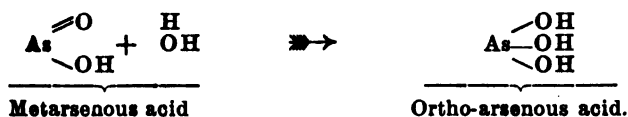
¹⁰ In the French Codex of 1866 there was official a *Poudre d' Acide Arsénieux*.

¹¹ See letters by Bernard Fantus, A. S. Loevenhart, and Torald Sollmann.

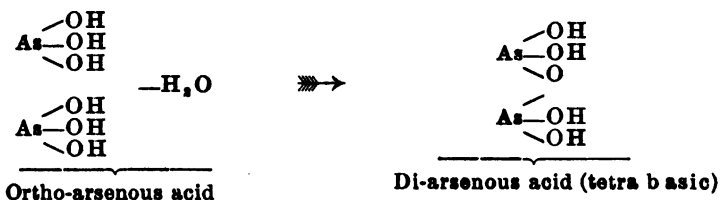
¹² See letter by Dr. Withering, in Fowler's Report, p. 124.

¹³ See letters by Dr. Fantus and Dr. Sollmann.

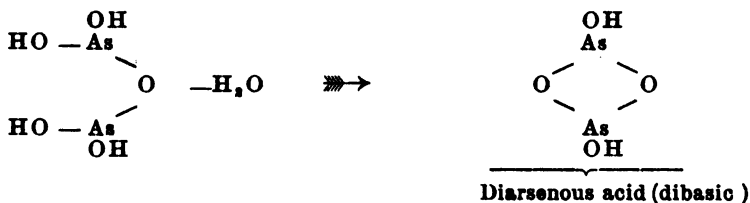
¹⁴ Similar formulas are used by A. Stavenhagen in his article on "Beitrag zur Kenntniss der Arsenite". Journ. pr. Chem. (1895) 159, p. 1.



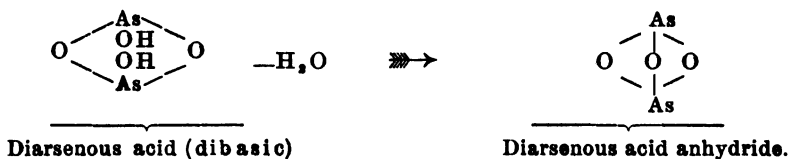
For a better understanding of the chemical possibilities of products obtained upon the evaporation of the solution of the arsenites, the following condensation products of ortho-arsenous acid with itself may be referred to.



Still another dehydration reaction may be indicated by the following formulas:



A trioxide of arsenic resulting upon complete dehydration of this dibasic diarsenous acid which, however, is different structurally, hence in its properties, from the compound with which we started out, readily follows:



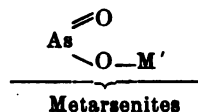
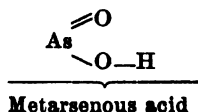
The possibilities of other hydration products of arsenic trioxide need not here be considered.

¹² Salts of this acid have been prepared by Stavenhagen, l. c.

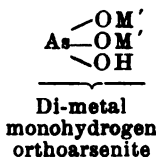
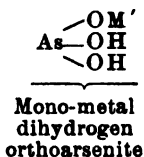
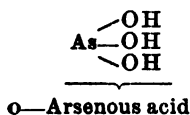
B. Action of Alkalies on Arsenous Acid.

Leaving out of consideration the diarsenous acid,¹⁶ as well as other possible polyarsenous acids, it is quite apparent

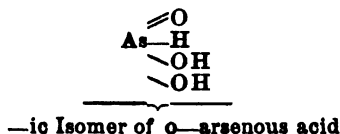
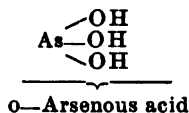
1.) That metarsenous acid is monobasic and with metals may be supposed to form the simple metarsenites:



2.) That orthoarsenous acid is tribasic and may be expected to form three types of orthoarsenites, viz.:



This leaves out of consideration, for the time at least, the possibility of the re-arrangement of the atoms of the orthoarsenous acid molecule made possible by a change of valence, such as that of the phosphorus, from three to five and the salts of the new ic acid.

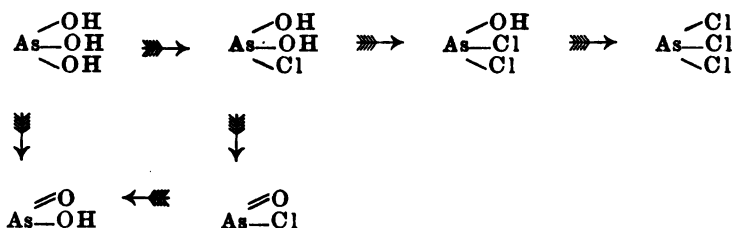


Which of the above salts are formed depends, in part at least, on the ratio of acid and alkali. Presumably a mixture, not a single compound results. As to which may dominate in the equilibrium resulting from a given formula for preparation need not be considered here, but will receive such attention as seems desirable, under the study of the pharmacopoeial formulas in use.

¹⁶ Pyroarsenites have also been prepared by Stavenhagen, l. c.

C. Action of Hydrogen Chloride on Arsenous Acid.

For the present purposes the diarsenous acids and other more or less complicated possibilities may be disregarded. Taking into consideration only the simple meta and orthoarsenous acids, the possibilities are indicated by the following structural formulas:



Again it becomes apparent that when arsenic trioxide is dissolved in water with the aid of hydrogen chloride, a number of products, rather than a single one, are likely to result and that the equilibrium, that finds its expression in a given pharmacopoeial preparation, will depend on a number of factors.

LIQUOR POTASSII ARSENITIS (FOWLER'S SOLUTION).

History.—The *arsenicum album*¹⁷ of the alchemists, the arsenous acid of the antiphlogistic nomenclature, our arsenic trioxide, appears first to be mentioned in the Latin alchemistic manuscripts formerly attributed to Geber.¹⁸ Under the ban of the phlogistic theory, it was regarded as the calx of the regulinic arsenic, a half metal (Brandt, 1733).¹⁹ This conception paved the way to the recognition of the "white arsenic" as an oxide of the element.²⁰ The differentiation of the two oxides as *acide arsénieux* and *acide arsénique* in accordance with the new nomenclature of Morveau, Lavoisier, Berethollet and Fourcroy (1787) naturally followed. The recognition of the several arsenous acids: ortho, meta and pyro and their several salts also of the isomeric trioxides came later.

¹⁷ So called to contrast it with *arsenicum citrinum* (auripigment) and *arsenicum rubrum* (realgar), Kopp, Geschichte der Chemie, vol. 4, p. 90.

¹⁸ Kopp, Geschichte der Chemie, vol. 4, p. 90; also E. v. Meyer, History of Chemistry (3rd ed.) p. 58.

¹⁹ Kopp, Geschichte der Chemie, vol. 4, p. 92.

²⁰ Kopp, Geschichte der Chemie, vol. 4, p. 99.

As already pointed out, the medicinal use of arsenic compounds was restricted largely to external purposes (depilatory, etc.). Whether arsenic, or more correctly, arsenous acid or its salts, or possibly organic derivatives of arsenic, played a role in the famous *Aqua tofana* of about 1700 may possibly never be definitely cleared up.²¹ That white arsenic combines with aqueous alkalies was shown by Macquer²² in 1746 and 1748, who called the products resulting *fois d' arsenic*, or arsenic liver, reminding of the times when arsenic was supposed to be similar to sulphur.²³

It was this property that Hughes, apothecary of the infirmary at Stafford, made use of when requested by Fowler to analyze and duplicate a quack remedy, known as "Tasteless ague or fever drops" which the latter had found efficacious in the "cure" of "agues, remitting fevers and periodic headaches".²⁴ This was in 1786. "It is universally recognized that Fowler introduced the modern medicinal employment of the arsenic, but it should in fairness be remembered that he was guided to his discovery by a quack remedy, as he himself fully acknowledged".²⁵

Fowler's solution quickly found its way into the pharmacopoeias: first of all into the London Pharmacopoeia of 1809.²⁶ From this it quickly passed into the first edition of the United States Pharmacopoeia which was published in 1822. On the European continent, it made its first appearance in the *Pharmacopoea Hanoverana* of 1819. Its rapid admission to the other state pharmacopoeias is indicated by the following chronological list:²⁷

- 1822 *Pharmacopoea Bavarica*
- 1823 *Pharmacopoea Belgica*
- 1826 *Codex Medicamentarius*

²¹ Comp. Peters, *Aus pharmazeutischer Vorzelt, neue Folge, zweite Aufl.*, (1899), p. 124.

²² See Kopp, *Geschichte der Chemie*, vol. 4, p. 95.

Macquer, *Dictionary of Chemistry*, pp. 648 and 666; Macquer however, does not differentiate between the potassium arsenite obtained by dissolving arsenic trioxide in potassium carbonate solution, and potassium arsenate, obtained by dissolving arsenic trioxide in aqueous potassium nitrate solution.

²³ A similarity that is even today reflected in the classification of minerals as illustrated by the isomorphous series of pyrites and arsenical pyrites.

²⁴ Wootton, *Chronicles of pharmacy*, vol. 2, p. 134; See also Wilson's patent in appendix.

²⁵ Wootton, p. 135.

²⁶ Powell's translation of the *Pharmacopoeia Londinensis*, 1809.

²⁷ Whether in all cases the date given is that of the first appearance has not been definitely settled because of the inability to consult complete sets of editions in all cases.

- 1827 *Pharmacopoea Borussica*
 1831 *Pharmacopoea Slesvico-Holsatica*
 1855 *Pharmacopoea Austriaca*
 1868 *Pharmacopoea Danica*

While Macquer,²⁸ who was professor of Medicine and Chemistry at the University of Paris, points out that only quacks used arsenic for internal administration, the regular medical practitioners of the infirmary of Stafford, England, used the "Tasteless ague and fever drops," a secret preparation,²⁹ during the years 1781, 1782, and 1783 as a remedy against intermittent fevers. This adoption of a "patent medicine"³⁰ by the physicians of the infirmary, caused the apothecary Hughes to analyse³⁰ and imitate³¹ this secret preparation, basing his experiments on the "pharmaceutic history" of arsenic found in Lewis's *Materia Medica*.³² Even of the milder sulphide minerals, Lewis makes the following statement: "The native minerals have been used as medicines in the eastern countries, and by some imprudently recommended in our own". (*Materia Medica*, p. 104.)

According to the account of Dr. Withering of Birmingham, this physician used a simple solution of *arsenicum album*, one grain to each ounce of distilled water, the solution being "facilitated by boiling for a minute or two in a Florence Flask, or other glass vessel". "Long continued boiling" he adds "disposes it to precipitate again".³³ The same formula was employed by Dr. Arnold of Leicester³⁴ who directs the solution to be filtered. While this solution was satisfactory in hospital practice, where the quantity

²⁸Dict. of Chemistry, p. 103: "Arsenic is a very violent corrosive poison: it produces always the most painful symptoms and fatal effects, whether it be taken internally or applied externally. It ought never to be employed medicinally, although some people not very intelligent, give small doses of it in obstinate intermittent fevers, which it effectually cures, but is always attended with bad consequences to the patients, such as phthisis, and other no less troublesome diseases."

²⁹Fowler, Medical Reports, Preface, p. vii.

³⁰Ibidem, Preface, p. vi; See also Wootton, On patent medicines in Appendix. Ibidem, p. 124, Withering, letter to Fowler.

³¹Ibidem, Preface, p. vii.

³²An *Experimental History of the Materia Medica of the Natural and Artificial Substances Made Use of in Medicine*. Containing A Compendious View of their Natural History, An Account of their Pharmaceutic Properties, And an Estimate of their Medicinal Powers, so far as they can be ascertained by Experience, or by rational Induction from their sensible Qualities. By William Lewis, London. 1761.

³³Fowler, Medical Reports, p. 124.

³⁴Ibidem, p. 117.

prepared was used up quickly, it did not suffice for private practice because precipitation took place upon standing. In order to overcome this, Mr. Baley, the apothecary of Birmingham, added "nitre" to the solution "by the direction of Mr. Hughes".²⁵ Fowler, in his report states that he used "fixed vegetable alkali".²⁶ At the same time he points out that the "fixed vegetable alkali" is not "perfectly pure; for that which is of the Druggists is frequently so impure, a double Proportion of purified nitre may be substituted" instead of going to the trouble of purifying the alkali.²⁷

We have, therefore, at the very beginning, when arsenical therapy was transferred from the secret practices of nostrum venders to the above board practice of the regular physician, three different pharmaceutical preparations:

- 1.) The simple solution of arsenic trioxide in water;
- 2.) The solution of arsenic trioxide in water with the aid of potassium carbonate, a chemical solution so-called with the formation presumably of a potassium arsenite;
- 3.) The solution of arsenic trioxide in water with the aid of potassium nitrate whereby presumably a potassium arsenate is formed.

All three solutions have found their way into pharmacopoeias or similar standards. Thus the simple solution of arsenic trioxide was official in the French Codex. That of the ratio of 1:1000 as *Soluté Arsenical ou Mineral* (Boudin) in 1884. A *Soluté Arsenical* Isnard, ratio 1:10000, is likewise mentioned by Dorvault in his *L'Officine* (1910), p. 1289. The solution of arsenic trioxide in aqueous potassium carbonate is the one that became official in most pharmacopoeias, with "Fowler's Solution" either as title or synonym. The third solution has become official as *Liquor Arsenicalis Clemens*, N. F., IV, though the oxidation is effected not by the nitric acid set free from the nitre, but by bromine. Similar sodium compounds are official as *Liquor Sodii Arsenatis*, U. S. P. and *Liquor Sodii Arsenatis*, Pearson, N. F., IV.

Names and Synonyms. The compound resulting upon the union of "white arsenic" (As_2O_3) and alkali in aqueous solution was named *fois d'arsenic*, liver of arsenic, by Macquer in 1776 because of the similarity of arsenic to sulphur which produced the so-called

²⁵ Ibidem, p. 125.

²⁶ Ibidem, Preface p. viii; also p. 79.

²⁷ Ibidem, pp. 82 and 83.

livers (liver of sulphur) under similar conditions. When Fowler prepared his arsenical solution in 1786, the new nomenclature of acids, bases and salts of Lavoisier and his committee of four (1787) had not been worked out. Moreover, he desired particularly to omit any reference to arsenic, hence he called his preparation "*Mineral Solution*".³⁸ Somewhat later the solution was merely known as *Liquor (solutio) arsenicalis* Fowleri and as such became official in the London Pharmacopoeia of 1809.

In the U. S. P. of 1820 the English title is still "*Arsenical solution*", but in the Latin title an attempt was made to make it conform with the new nomenclature of the antiphlogistic system of chemistry, hence *Liquor Potassae Arseniatis*.³⁹ Whether this should read *Arsenitis* and whether it is to be assumed that the additional "a" is due to a typographical error, it may be too late to ascertain. The 1830 Philadelphia edition makes the correction: *Liquor Potassae Arsenitis*, whereas the New York edition uses *Liquor Arsenicalis* as the official Latin title and *Solution of Arsenite of Potass.* as well as *Fowler's solution* as English synonyms for *Arsenical Solution*.

The change from the oxygen acid to the hydrogen acid nomenclature, viz. to *Liquor Potassii Arsenitis*, is made in 1870 and continues throughout after that date. Fowler's name appears only in connection with the synonyms for the New York 1830 edition and in the revisions of 1880, 1900 (index only) and 1910.

A list of recent pharmacopoeial titles follows with references to sources.⁴⁰

³⁸ In his report, preface page x, Fowler, makes the following statement: "— as the idea of poison seems to be so strongly connected with that of arsenic, it will be found to be very difficult to separate them in the mind, whenever that term is named; and therefore to correct as much as possible such disagreeable ideas, in the practice of the healing art, the medicine now about to be introduced to the notice of the public, will be distinguished by the name *Mineral Solution*."

³⁹ Up to the present date the British Pharmacopoeia refuses to apply a chemical designation to this solution, but calls it *Liquor Arsenicalis*. In commenting on the British usage the editors of the U. S. Dispensatory, 13th ed. in 1872, make the following statement: "The name by which this preparation is designated in the U. S. Pharmacopoeia is the most correct. It has however, been denied that the carbonate of potassa is decomposed by the arsenious acid, which is supposed to be merely held in solution; and, in this view of the nature of the preparation the British name *Arsenical Solution* would be appropriate."

⁴⁰ For non pharmacopoeial names and synonyms, likewise for older pharmacopoeial nomenclature see the glossary.

- Arsenikdropper*, Ph. Svenska (1908).
Arsenicalis Liquor Fowleri, Ph. Belg. (1906).
Arsenical Solution, Ph. B. (1914).
Fowler's Arsenikdraaper, Ph. Norv. (1913).
Fowlersche Loesung, P. G. (1910).
Fowler's Solution, U. S. P. IX.
Kalii arsenicosi liquor, Ph. Belg. (1906).
Kalium Arsenicosum solutum, Ph. Helv. (1907).
Licor Arsenical de Fowler, Ph. Hisp. (1905).
Liqueur Arsénicale de Fowler, Ph. Belg. (1906).
Liqueur de Fowler, Fr. Cod. (1908).
Liquor Arsenicalis, Ph. B. (1914).
Liquor Arsenicalis Fowleri, Ph. Norv. (1913).
Liquor Arsenicalis ex Fowler, Ph. Hisp. (1905).
Liquor Arsenicale del Fowler (F. I.), Ph. Ital. (1909).
Liquor Arsenitis Kalici, Ph. Svensky, (1908).
Liquor Arsenitis Kalici, Ph. Norv. (1913).
Liquor Fowleri, Ph. Norv. (1913).
Liquor Kalii arsenicosi, Ph. G. (1910).
Liquor Potassae arseniatis, U. S. P. (1820).
Liquor Potassii Arsenitis, U. S. P. (1916).
Potassium arsenit licuid, Ph. Roman. (1893).
Solucion de Arsenito Potasico, Ph. Hisp. (1905).
Soluté d' Arsénite de Potasse, Fr. Cod. (1908).
Solutio Arsenitis Kalii composita, Nedrl. Ph. (1898).
Solutio Arsenicalis Fowleri, Ph. Russ. (1910).
Solutio Kalii arsenicosi, Ph. G. (1910).
Solutio le arsenito de Potassa, Ph. Port. (1876).
Solution of Potassium Arsenite, U. S. P. IX.
Solutum Arsenitis Kalici, Ph. Port. (1876).
Solutum arsenitis potassici, Ph. Hisp. (1905).
Soluzione del Fowler, Ph. Helv. (1907).
Soluzione alcalina di metarsenito di potassio, Ph. Ital. (1909).

The London and British Pharmacopoeias afford an interesting example of apparent chemical misnomer. The Latin title of the 1809 London Pharmacopoeia, the first to make Fowler's solution official, is *Liquor Arsenicalis*. This title was used in the London Pharmacopoeia of 1824, but that of 1851 used the dualistic title *Liquor Potassae Arsenitis*. The British Pharmacopoeia re-

turned to the title *Liquor Arsenicalis*⁴¹ and has maintained it throughout its revisions; the title of the London Pharmacopoeia of 1851, viz. *Liquor Potassae Arsenitis* being used as a synonym.

If the official title is to be justified because we really know little about the exact chemistry of the solution, this excuse or line of reasoning will not hold when we study the English practice as to the designation of the principal ingredient of the solution. In the 1809 London Pharmacopoeia it was *Arsenici Oxidum Sublimatum*, hence in accordance with the dualistic nomenclature. Yet in 1824 it was changed back to *Arsenicum album sublimatum*. In 1851 it became *Acidum Arseniosum*, again in accordance with the dualistic nomenclature. But whereas the designation of 1809, viz. *Arsenici oxidum*, is indicative of a base, that of 1851, *Acidum Arseniosum*, is plainly indicative of an acid. It is possibly because of this that the phrase (*Acidum metallicum sublimation praeparatum*) is added in parenthesis. Whereas the element is still pronounced metallic in character, its oxide is now, not a base, but an acid.

A peculiar incongruity in spelling is found in the words arsenious and arsenite. The ending *ous* is that of the acid with lower oxygen content, and becomes *ite* for the salts thereof. The ending *ic* is that of acids of higher oxygen content and becomes *ate* for its salts. Hence arsenic should yield:

- A.) arsenous acid, and its salts should be arsenites; also
- B.) arsenic acid, and its salts should be arsenates.

However the former acid is commonly spelled arsenious acid (P. L. 1851; B. P. 1864, 1885, 1898, 1914.). Hence the salt should be arseniite, but almost invariably it is spelled without the second "i".⁴²

The English pharmacopoeias are not the only offenders in this direction. Roscoe and Schorlemmer, in their "Treatise on Chemistry", vol. II, p. 1246 (1911) still use arsenious acid and arsenites.

Our own Pharmacopoeias, after having clung to arsenious acid (Latin, *Acidum Arseniosum*) from 1820 to 1880 inclusive, in 1890 changed its spelling to Arsenous acid (Latin, *Acidum Arsenosum*), only to be changed in the subsequent editions to Arsenic Trioxide (Latin, *Arseni Trioxidum*).

⁴¹ "This appellation is certainly very objectionable, as it conveys an erroneous idea of the preparation, even admitting that the term arsenic may be used to designate the white oxide: it should have been *Liquor Arsenialis Potassae* or *Liquor alcalinus Oxidi Arsenici*". A. T. Thomson, The London Dispensatory, 4th edition, 1826.

⁴² The single exception observed thus far is found in the Norwegian Pharmacopoeia of 1918: *Liquor Arsenitis Kalici*.

PHARMACOPOEIAL TEXT. In as much as Fowler's solution was made official in the first edition of the U. S. Pharmacopoeia, was included in both the New York and Philadelphia editions of 1830, and has remained official up to the present time, there are eleven written texts to be considered. Moreover, the 1820 edition and both of the 1830 editions contain the text in both Latin and English. The detailed comments on the text, whether based on the study of the literature of the subject or on laboratory experiments or observations, are recorded in connection with those parts of the text to which they have reference. A better idea of this part may be had by a mere glance at the list of text subjects commented upon:

- 1.) Titles and Synonyms.
- 2.) Definition.
- 3.) Preservation.
- 4.) Arsenic trioxide as an ingredient.
- 5.) The form in which it is used.
- 6.) Potassium carbonate or bicarbonate as an ingredient.
- 7.) Ratio of ingredients.
- 8.) Water.
- 9.) Amount of water to effect solution.
- 10.) Solution of arsenic trioxide.
- 11.) Alcohol and compound tincture of lavender.
- 12.) Volume of finished product.
- 13.) Appearance of finished product.
- 14.) Qualitative tests.
- 15.) Assay.
- 16.) Dose.

NOTE. For convenient reference, the numbers representing the subjects commented upon are incorporated in the text proper.

LIQUOR POTASSAE ARSENIATIS¹ U. S. P. 1820*Ingredients.*

R. Acidi arseniosi,⁴ in pulverem
subtilem redacti;⁵
Potassae subcarbonatis,⁶ utri-
usque grana sexaginta qua-
tuor.⁷
Aquae distillatae⁸ octantem
unum.⁹

Directions.

In vase vitreo concoque donec
acidum arseniosum omne resolutum.¹⁰ Liquorem frige-
factum in
mensuram octariam infunde; et
adde

Alcoholis fluidrachmas quatuor,¹¹

Et aquae distillatae quantum
suffecerit ad mensuram complen-
dam.¹²

ARSENICAL SOLUTION¹*Ingredients.*

Take of Arsenious acid,⁴ in fine
powder;⁵
Subcarbonate of potass,⁶ each
sixty-four grains.⁷
Distilled water,⁸ one pint.⁹

Directions.

Boil them together in a glass
vessel until the arsenic is entirely
dissolved.¹⁰ When the solution is
cold, pour it into a pint measure,
and add thereto Alcohol,¹¹ four
fluidrachms, and so much distilled
water, as shall fill up the measure.¹²

LIQUOR ARSENICALIS¹ U. S. P. 1830 N. Y.*Ingredients.*

R. Acidi arsenici⁴ in pulverem
subtilem redacti,⁵
Potassae subcarbonatis,⁶ utri-
usque grana sexaginta qua-
tuor,⁷
Aquae distillatae⁸ octantem
unum,⁹
Alcoholis fluidrachmas qua-
tuor;¹¹

Directions.

In case vitreo concoque donec
acidum arseniosum omne resolutum.¹⁰

Liquorem frige-
factum in men-
suram octariam infunde; et adde
alcohol, et aquae distillatae quan-
tum suffecerit ad mensuram comp-
lendam.

ARSENICAL SOLUTION

Solution of Arsenite of Potass. Fowler's Solution¹*Ingredients.*

Take of Arsenious acid,⁴ in fine powder,⁵

Subcarbonate of potass,⁶ each sixty-four grains,⁷

Distilled water⁸ one pint,⁹

Alcohol, four fluidrachms,¹¹

Directions.

Boil them together in a glass vessel, until the arsenic is entirely dissolved.¹⁰ When the solution is cold, pour it into a pint measure, and add to it the alcohol and so much distilled water, as shall fill up the measure.¹²

LIQUOR POTASSAE ARSENITIS¹ U. S. P. 1830 Phila.*Ingredients.*

R. Acidi arseniosi⁴ in pulverem subtilissimum triti,⁵

Potassae Carbonatis Purissimi,⁶ singulorum, grana sexaginta quatuor;⁷

Aquae Destillatae⁸ quantum satis sit;

Spiritus Lavandulae Compositi fluidrachmas quatuor.¹¹

Directions.

Acidum Arseniosum et Potassae Carbonatem cum Aquae Destillatae octario⁹ coque, in vase vitreo, donec Acidum omnino liquetur.¹⁰

Liquori frigefacto adjice Spiritum Lavandulae, et postea Aquae Destillatae quantum satis sit ut mensuram octarii accuratè impleat.¹²

SOLUTION OF ARSENITE OF POTASSA¹*Ingredients.*

Take of Arsenious Acid,⁴ in very fine powder,⁵

Purest Carbonate of Potassa, each,⁶ sixty-four grains,⁷

Distilled Water a sufficient quantity;

Compound Spirit of Lavender four fluidrachms.¹¹

Directions.

Boil the Arsenious Acid and Carbonate of Potassa with a pint⁹ of Distilled Water, till the Acid is entirely dissolved.¹⁰ To the solution, when cold, add the Spirit of Lavender, and afterwards sufficient Distilled Water to make it fill up exactly the measure of a pint.¹²

LIQUOR POTASSAE ARSENITIS U. S. P. 1840

SOLUTION OF ARSENITE OF POTASSA¹*Ingredients.*

Take of Arsenious Acid,⁴ in small fragments,⁵

Pure Carbonate of Potassa, each,⁶ sixty-four grains;⁷

Distilled Water⁸ a sufficient quantity;

Compound Spirit of Lavender half a fluidounce.¹¹

Directions.

Boil the Arsenious Acid and Carbonate of Potassa with twelve fluidounces⁹ of Distilled Water, in a glass vessel, until the Acid is entirely dissolved.¹⁰ To the solution, when cold, add the Spirit of Lavender, and afterwards sufficient Distilled Water to make it fill exactly the measure of a pint.¹²

LIQUOR POTASSAE ARSENITIS U. S. P. 1850

SOLUTION OF ARSENITE OF POTASSA¹*Ingredients.*

Take of Arsenious Acid,⁴ in small fragments,⁵

Pure Carbonate of Potassa,⁶ each, sixty-four grains;⁷

Distilled Water⁸ a sufficient quantity;

Compound Spirit of Lavender half a fluidounce.¹¹

Directions.

Boil the Arsenious Acid and Carbonate of Potassa, in a glass vessel, with twelve fluidounces of Distilled Water, till the Acid is entirely dissolved.¹⁰ To the solution, when cold, add the Spirit of Lavender, and afterwards sufficient Distilled Water to make it fill exactly the measure of a pint.¹²

LIQUOR POTASSAE ARSENITIS U. S. P. 1860

SOLUTION OF ARSENITE OF POTASSA¹*Ingredients.*

Take of Arsenious Acid,⁴ in small pieces,⁵

Bicarbonate of Potassa,⁶ each, sixty-four grains;⁷

Compound Spirit of Lavender half a fluidounce;¹¹

Distilled Water⁸ a sufficient quantity.

Directions.

Boil the Arsenious Acid and Bicarbonate of Potassa, in a glass vessel, with twelve fluidounces⁹ of Distilled Water till the Acid is entirely dissolved.¹⁰ To the solution, when cold, add the Compound Spirit of Lavender, and afterwards sufficient Distilled Water to make it measure a pint.¹²

LIQUOR POTASSII ARSENITIS U. S. P. 1870

SOLUTION OF ARSENITE OF POTASSIUM¹*Ingredients.*

Take of Arsenious Acid,⁴ in small pieces,⁵

Bicarbonate of Potassium,⁶ each, sixty-four grains;⁷

Compound Spirit of Lavender half a fluidounce;¹¹

Distilled Water⁸ a sufficient quantity.

Directions.

Boil the Arsenious Acid and Bicarbonate of Potassium, in a glass vessel, with half a fluidounce⁹ of Distilled Water, until the Acid is entirely dissolved,¹⁰ and add twelve fluidounces of Distilled Water. Then add the Compound Spirit of Lavender, and afterwards enough Distilled Water to make it measure a pint.¹²

LIQUOR POTASSII ARSENITIS U. S. P. 1880

SOLUTION OF ARSENITE OF POTASSIUM

[FOWLER'S SOLUTION.]¹

Arsenious Acid, ⁴ in small pieces, ⁵ <i>one part</i> ¹	1
Bicarbonate of Potassium, ⁶ <i>one part</i> ¹	1
Compound Tincture of Lavender, ¹¹ <i>three parts</i>	3

Distilled Water,⁸ *a sufficient quantity*,

To make *one hundred parts*¹²..... 100

Boil the Arsenious Acid and Bicarbonate of Potassium in a glass vessel with *ten (10) parts*⁹ of Distilled Water, until the Acid is completely dissolved.¹⁰ Then add the Compound Tincture of Lavender, and enough Distilled Water to make the product weigh *one hundred (100) parts*. Lastly, set the mixture aside for eight days and then filter through paper.³

If 24.7 Gm. of the Solution are boiled with 2 Gm. of bicarbonate of sodium, the liquid, when cold, diluted with 100 C.c. of water, and some gelatinized starch added, should require from 48.5 to 50 C.c. of the volumetric solution of iodine, before the blue color ceases to disappear on stirring (corresponding to 1 per cent. of arsenious acid of the required purity).¹³

LIQUOR POTASSII ARSENITIS U. S. P. 1890

SOLUTION OF POTASSIUM ARSENITE

[FOWLER'S SOLUTION.]¹

Arsenous Acid, ⁴ in fine powder, ⁵ <i>ten grammes</i> ¹	10 Gm.
Potassium Bicarbonate, ⁶ <i>twenty grammes</i> ¹	20 Gm.
Compound Tincture of Lavender, ¹¹ <i>thirty cubic centimeters</i>	30 Cc.
Distilled Water, ⁸ <i>a sufficient quantity</i> ,	

To make *one thousand cubic centimeters*¹²..... 1000 Cc.

Boil the Arsenous Acid and Potassium Bicarbonate with *one hundred (100) cubic centimeters*⁹ of Distilled Water, until solution has been effected.¹⁰ Then add enough Distilled Water to make the solution, when cold, measure *nine hundred and seventy (970) cubic centimeters*, and, lastly, add the Compound Tincture of Lavender. Filter through paper.

If 24.7 Cc. of the Solution be boiled for a few minutes with 2 Gm. of sodium bicarbonate, and the liquor, when cold, diluted with water to 100 Cc., and mixed with a little starch T.S., it should require from 49.4 to 50 Cc. of decinormal iodine V.S. to produce the blue tint of iodide of starch (corresponding to 1 Gm. of arsenous acid in 100 Cc. of the Solution).¹⁵

LIQUOR POTASSII ARSENITIS U. S. P. 1900

SOLUTION OF POTASSIUM ARSENITE¹

An aqueous solution, which should contain Potassium Arsenite corresponding in amount to 1 percent. of arsenic trioxide.²

Arsenic Trioxide, ⁴ in fine powder, ⁵ <i>ten grammes</i> ¹	10 Gm.
Potassium Bicarbonate, ⁶ <i>twenty grammes</i> ¹	20 Gm.
Compound Tincture of Lavender, ¹¹ <i>thirty grammes</i>	30 Gm.
Distilled Water, ⁸ <i>a sufficient quantity</i> ,	

To make *one thousand grammes*¹²..... 1000 Gm.

Boil the Arsenic Trioxide and Potassium Bicarbonate, in a tared dish, with *one hundred grammes*⁹ of Distilled Water, until solution has been effected.¹⁰ Then add enough Distilled Water to make the solution weigh *nine hundred and seventy grammes*, and, lastly, add the Compound Tincture of Lavender. Filter through paper.

If 24.6 Gm. of Solution of Potassium Arsenite be diluted with water to 100 Cc., the mixture very slightly acidified with diluted hydrochloric acid, and then made alkaline with 2 Gm. of sodium bicarbonate, it should require not less than 50 Cc. of tenth-normal iodine V.S. to produce a permanent yellow tint (corresponding to 1 Gm. of arsenic trioxide in 100 Gm. of the Solution).¹⁵

Average dose.—0.2 Cc. (3 minims).¹⁶

LIQUOR POTASSII ARSENITIS U. S. P. 1910

SOLUTION OF POTASSIUM ARSENITE

Liq. Pot. Arsen.—Fowler's Solution *Liquor arsenicalis Fowleri* P.I.

An aqueous solution containing potassium arsenite, corresponding in amount to not less than 0.975 per cent. nor more than 1.025 per cent. of As_2O_3 (197.92).² Preserve the Solution in amber-colored bottles.³

ARSENIC TRIOXIDE, ⁴ in fine powder, ⁵ <i>ten grammes</i> ⁷	10 Gm.
POTASSIUM BICARBONATE, ⁶ <i>twenty grammes</i> ⁷	20 Gm.
COMPOUND TINCTURE OF LAVENDER, ¹¹ <i>thirty grammes</i>	30 Gm.
DISTILLED WATER, ⁸ <i>a sufficient quantity</i> , ⁹	
To make <i>one thousand grammes</i> ¹²	1000 Gm.

Boil the arsenic trioxide and potassium bicarbonate in a tared flask with *one hundred grammes* of distilled water, until solution has been effected,¹⁰ and then add enough distilled water to make the solution weigh *nine hundred and seventy grammes*; then add the compound tincture of lavender and filter through paper.

Solution of Potassium Arsenite is a clear or faintly opalescent liquid with a pink color and a slight odor of lavender.¹³ It is alkaline to litmus.¹⁴

Acidulate strongly 10 mls of the Solution with hydrochloric acid and add an equal volume of hydrogen sulphide T.S.; a yellow precipitate is produced which dissolves in ammonium carbonate T.S.¹⁴

Acidulate 4 mls of Solution of Potassium Arsenite with diluted nitric acid, add 1 mil of silver nitrate T.S. and superimpose a layer of ammonia water upon this liquid; no red or reddish-brown color is observed at the line of contact (*arsenate*).¹⁴

Assay—Dilute about 20 mls of Solution of Potassium Arsenite, accurately weighed, with 75 mls of distilled water, acidify the mixture very slightly with diluted hydrochloric acid, then dissolve in the solution 2 Gm. of sodium bicarbonate and titrate the resulting liquid with tenth-normal iodine V.S., starch T.S. being used as indicator. It shows not less than 0.975 per cent. nor more than 1.025 per cent. of As_2O_3 .¹⁵

Each mil of tenth-normal iodine V.S. used corresponds to 0.004948 Gm. of As_2O_3 . Each gramme of Solution of Potassium Arsenite corresponds to not less than 1.97 nor more than 2.07 mls of tenth-normal iodine V.S.¹⁵

AVERAGE DOSE—Metric, 0.2 mil—Apothecaries, 3 minims.¹⁶

COMMENTS ON U. S. P. TEXT

1.) *Titles and Synonyms.* See Names and Synonyms.

2.) *Definition.* A definition is not given previous to 1900. The modification in the definition for 1910 was necessitated by the Pure Food and Drugs Act of 1906 which demanded reasonable limits rather than an absolutely fixed standard.

3.) *Preservation.* The 1910 revision is the only one that directs that the solution be kept in amber colored bottles to protect it against light.

Fowler's Solution upon standing deposits a flocculent precipitate. This precipitate has apparently introduced a problem for comments and criticisms as to the cause, the composition and the ways and means of eliminating this objectionable factor. Unfortunately much of the work contributed on this topic is merely theoretical and not the result of experimental labor, at least no data of an experimental type are given in the majority of papers published.

The causes for this precipitate as given, may be considered under three groupings:

1st. The action of certain organisms in the water, resulting in an algaecous growth.

2nd. The action of the alkali on the glass container.

3rd. The action of the alkali on one or more of the ingredients of the alcoholic tincture or spirit used.

Those supporting the first theory are: J. Mueller⁴³ who suggests the addition of 0.4 p. c. of borax, as a preservative; Perschne⁴⁴ who suggests the use of glycerin for the same purpose; Kollo⁴⁵ and Benysek⁴⁶ who claim that the alcohol present acts as a preservative;⁴⁷ while Feuer⁴⁸ considers its preservative action negligible; and Dannenberg⁴⁹ who speaks of the precipitate as an algaecous growth. Brautigam⁵⁰ apparently disagrees with the above, in his claim that the precipitate is not an algaecous growth but results from the action of the alkali on the glass container. This is supported in part by Neinhans⁵¹ who calls attention also, to the U. S. P.

⁴³ Am. Jour. Pharm., 51, p. 249; from Pharm. Ztg. (1879.)

⁴⁴ Am. Journ. Pharm., 55, p. 456; from Pharm. Ztschr. f. Russland (1887.)

⁴⁵ Pharm. Post, 29, p. 233 (1896.)

⁴⁶ Pharm. Post., p. 157 (1896.), see also *ibid.* 32, p. 49.

⁴⁷ Presumably the preservative action of the alcohol tends to prevent the growth of organisms that result in the formation of a flocculent mass.

⁴⁸ Pharm. Post., 25, p. 331 (1895.)

⁴⁹ Pharm. Centralh., 22, p. 319 (1881.)

⁵⁰ Pharm. Centralh., 33, p. 324 (1892.)

⁵¹ Pharm. Ztg., 37, p. 331 (1892.)

of 1880 which directed that the solution be filtered after standing eight days, to remove the precipitate formed. The editor of the *Chemiker Zeitung*⁵³ calls attention to a previous custom of neutralizing the excess alkali with acetic acid⁵⁴ to prevent this same reaction. Evidently in a parallel line of thought Garraud⁵⁴ suggests using a standard alkali⁵⁵ to avoid excess alkalinity in the finished product.

Seemingly most writers support the third theory, viz. the action of the alkali on the ingredient or ingredients of the alcoholic tincture or spirit used. M. Goeldner⁵⁶ suggests the use of phenolphthalein as coloring agent in place of such a pigment as that of red saunders of the compound tincture of lavender, evidently assuming that the alkali and the pigment from the red saunders cause the precipitate. J. Luettker⁵⁷ attributes the "dirty color" appearing in the P. G. solution to the action of the alkali and compound spirit of melissa⁵⁸ and suggests avoiding this by neutralizing the solution. Nienhaus⁵¹ claims that the alkali and aromatic tinctures and even distilled spirits used in the various pharmacopoeias are the main causes of the precipitate. He substitutes melissa water for the alcoholic distillate in the P. G. solution, and does not obtain a precipitate. The substitution of compound spirit of melissa by melissa water is also recommended by Pascal⁵⁹ and Menhaus,⁶⁰ while Mueller^{60a} suggests using the simple spirit of melissa. An unsigned article⁶¹ states that the precipitate is due to the action of the excess alkali on the red saunders. The "query" editor of the *Druggists Circular*⁶² suggests all of the already men-

⁵³ Chem. Ztg., 16, p. 174 (1892.)

⁵⁴ To what extent the solution is neutralized is not made clear. As the alkalinity of the solution is supposed to be, in part, due to the hydrolysis of the formed arsenite (see qualitative tests No. 13) a complete change to potassium acetate might take place if sufficient acid were added, before the solution would respond to a "neutral test."

⁵⁵ Pharm. Ztg., 39, p. 753; from Bull. Soc. Pharm. de Bordeaux (1894.)

⁵⁶ Here again the alkalinity due to any potassium arsenite present has been overlooked, apparently, or it has been assumed that the alkalinity is negligible.

⁵⁷ Ber. d. Pharm. Gesellch., 2, p. 127 (1892.), see also p. 302.

⁵⁸ Pharm. Centralh., 559 (1890.)

⁵⁹ Compound Spirit of Melissa P. G. is prepared by macerating a mixture of melissa leaves, lemon peel, nutmeg, cinnamon and cassia buds with hydro-alcohol and subsequently distilling until a definite amount of distillate has been obtained. This spirit apparently contains only volatile matter as compared with the Compound Tincture of Lavender U. S. P. which is prepared by maceration and filtration.

⁶⁰ Pharm. Ztg., 50, p. 1009 (1905.), from Bull. Commercial.

^{60a} Nat. Drug., 21, p. 22 (1892.)

⁶¹ Ber. d. pharm. Ges., 2, p. 302 (1892.)

⁶² Proc. A. Ph. A., 46, p. 694 (1896.) from Merck's Report

⁶³ Drug. Cir., 52, p. 223 (1908.)

tioned reasons and adds the possible insoluble impurities in the arsenic trioxide used. The impurities in the arsenic trioxide used are also emphasized by Gluecksmann.⁶³ Chumaceiro⁶⁴ refers to the "International Formula"⁶⁵ for preparing a clear permanent solution. This evidently eliminates the alkalinity. Moreover this formula directs that spirit of lavender be used in place of the tincture. However the finished product in this case is not a solution of an arsenite.⁶⁵

The strength of Fowler's Solution is based on the arsenic trioxide content. That a gradual oxidation of the trivalent arsenic to the pentavalent arsenic takes place is generally accepted. The cause of this oxidation however, has called forth some considerable investigation and comment. Apparently all investigators agree that the introduction of atmospheric oxygen, in various ways, is the direct cause, but the conditions which accelerate or retard such oxidation seem to offer a source of disagreement. G. Kassner⁶⁶ attributes the oxidation to the introduction of atmospheric oxygen, but does not mention any conditions influencing the rate. C. Feuer⁶⁷ claims that the oxidation due to atmospheric oxygen is slight within a half year's time, and that the alkalinity of the solution accelerates this change. Rosenthaler⁶⁸ merely points out that oxidation of arsenous acid takes place. Lyons⁶⁹ claims that under like conditions the greatest amount of oxidation takes place in an alkaline solution, the least in an acid solution, while in a solution containing the (HCO_3) radicle the rate of oxidation lies between the two. In a later publication Lyons⁷⁰ claims that no oxidation takes place in an acid solution. L. A. Brown⁷¹ suggests keeping the solution in small well filled and closed containers to prevent

⁶³ Pharm. Post., 29, p. 353 (1896.)

⁶⁴ Ibid. 52, p. 323 (1908.)

⁶⁵ According to the "International Formula" as given in this article, "spirit of lavender (colorless distillate)" is used in place of the Compound Tincture of Lavender U. S. P. Also some diluted hydrochloric acid is added, 3.5 grams (13.67 p. c.) to 1 gram of potassium carbonate. This represents 0.458 grams HCl , which requires 1.72 grams of potassium carbonate for neutralization. As only 1 gram of potassium carbonate is used evidently the finished product is an acid solution.

⁶⁶ Pharm. Ztg., 34, p. 419 (1889.)

⁶⁷ Pharm. Post., 28, p. 381 (1895.)

⁶⁸ Pharm. Centralh., 47, p. 850 (1906.)

⁶⁹ Proc. A. Ph. A., 56, p. 901 (1908.)

⁷⁰ Proc. A. Ph. A., 57, p. 904 (1909.)

⁷¹ Ky. Agr. Exp. Sta. Bull. No. 150, p. 153 (1910.)

oxidation. A. N. Cook⁷² attributes the oxidation to the atmospheric oxygen which is introduced every time the container is opened to remove some of the liquid. E'we and Vanderkleed⁷³ state that, "One sample of liquor potassium arsenite U. S. P. suffered an oxidation of 1.9 p. c. of its As_2O_3 as arsenite to arsenate in two years and three months. Another sample had 1.8 p. c. of As_2O_3 as arsenite oxidized to arsenate in one year and five months". Engelhardt and Winters,⁷⁴ after determining the amounts of arsenate and arsenite respectively during a period of 14 months conclude that only a slight amount of oxidation takes place in the solution.

4.) *Arsenic Trioxide as an Ingredient.* The original formula of Fowler calls for *arsenicum album* or "white arsenic", in which manner the arsenic trioxide was distinguished from the yellow and red sulphides. The London Pharmacopoeia of 1808 calls for *Arsenici oxidum sublimatum*. The U. S. P. of 1820 adopted the designation *arsenious acid* in accordance with the new antiphlogistic nomenclature. For other changes, see Names and Synonyms.

5.) *The Form in Which it is Used.* Fowler directs the "white arsenic" to be used "in pulverum subtilissimum triti, i. e. "trituated to a very fine powder". The U. S. P. of 1820 directs that the "arsenious acid" be used in form of a "fine powder"; the Philadelphia edition of 1830 directs a "very fine powder". "Small fragments" are suggested by the New York edition of 1830, also by the editions of 1840, 1850, 1860 and 1870. From 1880 on a "fine powder" is again directed.

The explanation for this is found in the following statement made by the editors of the U. S. Dispensatory, 13th ed. (1872), p. 1267: "In making this preparation, care should be taken that the arsenious acid is pure. This object is best secured by using the acid in small pieces instead of in powder. Sulphate of lime is a common impurity in the powdered acid, and if present will remain undissolved, and cause the solution to be weaker than it should be".

Although the U. S. P. of 1870 directs a qualitative test (complete volatilization) to be made, that would bar such an impurity as sulphate of lime, the U. S. P. of 1880 is the first to direct the assay of "arsenious acid". It is, no doubt, due to this difference in the requirements of the 1880 edition and its precursors from

⁷² Rep. So. Dak. F. & D. Com., 1912, p. 75 (1912.)

⁷³ Proc. Pa. Ph. Assn., 37, p. 277 (1914.)

⁷⁴ Jour. A. Ph. A., 6, p. 134 (1917.)

1840 on that the "fine powder" is again directed to be used in 1880.

6.) *Potassium Bicarbonate or Carbonate as an Ingredient.* Fowler calls it *Sal alkalinum fixum vegetabilis* or "salt of fixed vegetable alkali" to differentiate it from the fixed mineral alkali or sodium carbonate and the volatile alkali or ammonium carbonate. The designation of the U. S. P. 1820 is in accordance with the antiphlogistic nomenclature. The alkali used to facilitate the solution of the "arsenious acid" varies. According to the U. S. P. 1820 and the New York edition of 1830 it is *Potassae subcarbonas* or "Subcarbonate of potass.", which according to the 1820 edition is the "Impure subcarbonate of potass." or "Pearl ash". The Philadelphia edition of 1830 designates that "Purest Carbonate of Potassa" or *Potassae Carbonas Purissimus* be used, which is to be prepared from potassium bitartrate by ignition and lixiviation. (p. 172, not that in the *Materia Medica* list p. 20.) The editions of 1840, 1850 and 1860 direct that a "pure" carbonate be used. According to the 1840 edition this is prepared from the bitartrate, according to the 1850 and 1860 editions, by heating the bicarbonate. From 1870 the bicarbonate is directed to be used in the formula. Upon heating, as directed, the pure bicarbonate is changed to the pure carbonate.

7.) *Ratio of Ingredients.* Not only the ratio, but the exact quantities, viz. 64 grains of both the acid and alkaline ingredients, are the same in all editions of the U. S. P. up to 1870 inclusive, as they are in the original formula of Fowler. This would seem quite rational but for two considerations, viz.:

1. The purity of the potassium carbonate originally employed, no doubt, varied greatly. (For details of this see No. 6.)

2. In the 1870 edition, bicarbonate of potassium was substituted for carbonate, but the amounts (64 grains of each) remained the same.

Hence the ratio of acid (anhydride) to alkali (carbonate or bicarbonate) fluctuated greatly in the several revisions from 1820 to 1870 inclusive. Although the U. S. P. 1880 is a relatively modern treatise, as compared with its immediate precursors, the ratio was not changed in 1880, but the change was made in 1890, so that since that date the alkalinity of Fowler's Solution was once more what it may be supposed to have been originally, provided, however, that the "alkaline vegetable salt" of Fowler's formula was

pure potassium salt, which, in all probability it was not. In as much as it is impossible to establish the purity of the potassium carbonate used in the original formula, it would be vain to attempt to duplicate, in this respect, the original formula.

It might be argued that the "white arsenic" of Fowler's days was not as pure as the present pharmacopoeial product is supposed to be, and that the impurities in both ingredients compensated each other. However, it is scarcely to be assumed that the "white arsenic" or arsenic trioxide was ever as impure as the potassium carbonate made from wood ashes, unless it was wilfully adulterated. (For table of ratios see Number 12.)

8.) *Water.* According to his original formula, Fowler demanded "distilled well water". This is probably the reason why distilled water has always been demanded by the U. S. P.⁷⁵ A permanently hard water might be considered as interfering with the desired alkalinity of the finished product.⁷⁶

9.) *Amount of Water Used to Effect Solution.* According to Fowler's original formula only "a half pound" of water, necessary for the finished preparation, was used to effect the solution. The London Pharmacopoeia of 1809, also the U. S. P. of 1820 directed "one pint" to be used, the loss resulting from evaporation to be made up. So did both editions of 1830. The edition of 1840 reduced the amount to "twelve fluid-ounces", as did the editions of 1850, 1860 and 1870. In the 1880 edition, the amount was reduced much more, namely to one-tenth of the volume of the finished product. Practically the same ratio obtained in the editions of 1890, 1900 and 1910. The London Pharmacopoeia throughout made no reduction. However, the first British Pharmacopoeia in 1864 reduced the amount, prescribing 10 ounces to be used, likewise the edition of 1885. The 1898 edition directed either 10 ounces or 500 cc., depending upon whether the metric formula or the apothecaries formula was used as both were given in this edition. The 1914 edition prescribes 500 cc. In all B. P. formulas the amount of water directed to be used to effect solution is equal to one-half of the volume of the finished product.

⁷⁵ The several editions of the London and British pharmacopoeias, also the recent editions of all other pharmacopoeias consulted demand distilled water.

⁷⁶ Such a water, which, however, no pharmacist would think of using, is the public spring water of Sheboygan, Wis. It contains per liter 0.2394 Mg. equiv. $1.358 \text{ K}_2\text{CO}_3$, and 1.0832 Ca. equiv. $3.448 \text{ K}_2\text{CO}_3$, or a total of $4.806 \text{ K}_2\text{CO}_3$. Hence of the $13.804 \text{ K}_2\text{CO}_3 = 20.000 \text{ KHCO}_3$ used, about $9.000 \text{ K}_2\text{CO}_3$ remain for the solution of the 10 gm. As_2O_3 and the desired surplus alkalinity.

It has been commonly assumed that the original amount of water used was reduced for the purpose of accelerating the reaction between the acid and the alkali carbonate and thus increasing the rate of solution. Thus E. Martin⁷⁷ modified the U. S. P. process by dissolving 64 grains each of arsenic trioxide and potassium bicarbonate in two or three drams of water with the aid of heat. When solution was effected he added the remainder of the water. This procedure he claimed decreased the time ordinarily required to make Fowler's solution. G. Hamel⁷⁸ placed the arsenic trioxide and potassium carbonate, (3 grams each) in a test tube moistened the mixture with a few drops of water and applied heat until a liquid mass resulted. This he then diluted with a few mls of water and heated until solution took place, after which more water was added, up to the required volume. P. Maysse⁷⁹ modified the "Codex" method by heating one gram each of arsenic trioxide and potassium carbonate with five drops of water, in a test tube, until the solution took place and then diluting up to 100 cc.

In order to test the correctness of this explanation, experiments on the rate of solution in varying concentrations were performed.

A.) One gram of arsenic trioxide and two grams of potassium bicarbonate (the ratio of As_2O_3 and $KHCO_3$ used in the U. S. P.), were mixed with 25 mls, 50 mls, 100 mls, and 200 mls respectively, of boiling water, and the time required to obtain a clear solution noted. The effervescence, caused by the decomposition of the bicarbonate, had a tendency to carry the arsenic trioxide up the sides of the container, hence to interfere with the action of the solvent, even though a stirrer was used and vigorously at that.

To eliminate this objectionable feature the following modification was adopted. The potassium bicarbonate was dissolved in water, (20 gm. in sufficient water to make 100 mls.) and the solution boiled until no more carbon dioxide was apparently given off. This required about 30 minutes. An aliquot portion of this solution, representing the amount of potassium acid carbonate desired, was diluted with water up to a definite volume and the mixture heated to boiling. The required weight of arsenic trioxide was introduced into a test tube of suitable capacity, the boiling solution of the potassium salt poured on to this and the tube immediately im-

⁷⁷ Am. Jour. Pharm., 44, p. 202 (1872.)

⁷⁸ Pharm. Ztg., 51, p. 402 (1906.)

⁷⁹ Bull. des sc. pharmacol. 13, p. 106 (1906); through Digest of Comments, 1906.

mersed into a bath of boiling water. The mixture was constantly agitated and the time required to obtain a clear solution was recorded. Three separate determinations were made for each dilution. The results are recorded in the following table:

TABLE I.

1 Gm. As_2O_3	to	2 Gm. KHCO_3	
Volume (mils)	25	50	100
Time (minutes)	1,2,2	2,3,3	2,3,3

A glance at the table reveals the fact that the differences for the several dilutions are no greater than those obtained from the same dilution, hence fall within the limits of experimental error.

B.) In the next series an attempt was made to secure more satisfactory results by increasing the amounts of the chemical agents acting upon each other. Ten grams of arsenic trioxide and the equivalent 20 grams of potassium bicarbonate (as carbonate) with varying amounts of water were used. In this series one experiment only was performed with each volume of water. The results are herewith tabulated.

TABLE II.

10 Gm. As_2O_3	to		20 Gm. KHCO_3				
Volume (mils)	25	50	100	200	300	400	1000
Time (minutes)	3	4	3	5	3	4	3.5

Again the results tend to disprove the assumption that, with proper conditions, the rate of solution is hastened to any appreciable extent by greater concentration.

C.) A third series was made in an attempt to note the effect of the effervescence (mentioned in the preliminary experiments), when larger quantities of reagents were used. Ten grams of arsenic trioxide and 20 grams of potassium bicarbonate were mixed with 25 mils, 50 mils and 100 mils of boiling water, and the time of solution determined as before. The results are again tabulated.

TABLE III.

10 Gm. As_2O_3	to	20 Gm. KHCO_3	
Volume (mils)	25	50	100
Time (minutes)	4	6.5	5

The slight increase in time is, no doubt, due principally to the removal of the arsenic trioxide from the solution by the escaping carbon dioxide.

D.) In a fourth series of tests ten grams of arsenic trioxide and 11.2 grams of potassium hydroxide, the equivalent of 20 grams of potassium acid carbonate, the latter dissolved in 25 mils, 50 mils and 100 mils respectively, of boiling water, were mixed, and the time required for solution noted as above. In each case the time was not more than one minute. Apparently the arsenic trioxide dissolved as fast as it came in contact with the solvent quite irrespectively of the degree of concentration of the alkaline solvent.

10.) *Solution of Arsenic Trioxide.* For the chemistry of the solution see *Hydration of Arsenic trioxide*.

The formula for potassium arsenite given in the U. S. P. IX is KAsO_2 , potassium metarsenite. Whether it is assumed that the salt exists as the metarsenite in the official solution is not made clear. Apparently writers differ as to the composition of the arsenite in the solution. L. Bullock⁸⁰ speaks of the "chemically indefinite liquor arsenicalis," M. H. Buignet⁸¹ suggests that only part of the arsenous acid is combined with the alkali, the remainder being in simple solution. H. K. Bamber⁸² concludes that a reaction takes place between potassium carbonate and arsenous acid in preparing the solution, basing his conclusions on the fact that carbon dioxide was given off during the process. This drew forth a number of comments by Redwood, Garrod, Attfield and others as to its correctness, the main criticism being that the concentrations of Bamber's experiments were not comparable to the pharmacopoeial conditions. A. F. Haselden⁸³ refers to the controversy relating to the correctness of the title "arsenite of potash" or

⁸⁰ Pharm. Jour., 10, p. 357 (1850.)

⁸¹ Jour. de Pharm. et de Chim., 59, p. 439 (1856.)

⁸² Pharm. Jour., 17, p. 481 (1858.)

⁸³ Pharm. Jour., 16, p. 541 (1857.)

"Liquor Arsenicalis." O. Olberg⁸⁴ offers a formula for the solution in which he substitutes potassium hydroxide for the potassium bicarbonate. In this solution he claims that the arsenite exists as the di-potassium-mono-hydrogen-ortho-arsenite, K_2HAsO_3 . After determining the amount of potassium arsenite formed when 5 grams each of arsenous acid and potassium carbonate were heated in the presence of water, for varying intervals, C. Lonnes⁸⁵ concludes that the title "Liquor Kali Arsenicosi" is a misnomer, and that "Liquor arsenicalis" is more correct. L. H. Bernegau⁸⁶ states that the metarsenite is formed when arsenic trioxide and potassium bicarbonate are heated gently in the presence of water, (presumably as in the U. S. P. process), but that the dry salt has the formula, (according to Schmidt), of $KAsO_3$, $HAsO_3 + H_2O$. L. H. Bernegau⁸⁷ also reports that the dry salt always contains some uncombined potassium carbonate. Stocker⁸⁸ in his discussion on the P. G. solution points out that the amount of potassium carbonate prescribed is insufficient to saturate all of the arsenic trioxide. J. Ziegler⁸⁹ disagrees with Stocker on this point as does Schenk.⁹⁰ The *Commentar zum D. A.-B. V.*⁹¹ states that the alkalinity of Fowler's solution is due in part to the excess of potassium carbonate present. This would also tend to agree with Ziegler towards invalidating Stocker's claim.

In an attempt to determine whether a reaction takes place, towards the formation of an arsenite in Fowler's solution, the following experiments were performed.

I.) The solutions resulting from the rate of solution experiments were reserved for further observations. Twenty-four hours after their preparation a deposit of crystals was noticed in the solution representing the greatest concentration. These crystals were separated from the mother liquor by means of a force filter and freed from adhering liquid as much as possible by pressing between bibulous paper. Both crystals and mother liquor were assayed for

⁸⁴ The Apothecary, 2, p. 1 (1892.)

⁸⁵ Pharm. Ztg., 39, p. 90 (1894.)

⁸⁶ Am. Jour. Phar., 79, p. 553 (1907.)

⁸⁷ Proc. Pa. Ph. Ass'n., 33, p. 145 (1910.)

⁸⁸ Apoth. Ztg., 26, p. 335 (1911.)

⁸⁹ Apoth. Ztg., 26, p. 40 (1911.)

⁹⁰ Apoth. Ztg., 26, p. 379 (1911.)

⁹¹ Kommentar zum Deutschen Arzneibuch, 5 Ausgabe, 1910, p. 64 by O. Anselmino and Ernst Gllg.

potassium acid carbonate and arsenic trioxide, using N/1 acid and N/10 iodine respectively. The following results were obtained:—

Crystals	Wt. 7.6 gm.	67. p. c. KHCO_3	4.5 p. c. As_2O_3
Liquid	24.0 gm.	39.4 p. c. K_2CO_3	35.5 p. c. As_2O_3

II.) The experiment was repeated using 200 grams of potassium acid carbonate dissolved in 250 mls of water, and boiled for about thirty minutes. While boiling, this solution was added to 100 grams of arsenic trioxide contained in a flask and the whole immersed in a bath of boiling water until a clear solution resulted. The solution was allowed to stand over night when the crystals were collected and assayed as before. A duplicate experiment was made. The following results were obtained:—

Crystals	81. gm.	96. p. c. KHCO_3	1.7 p. c. As_2O_3
Liquid	359. gm.	{ 3.6 p. c. KHCO_3 22.1 p. c. K_2CO_3	20. p. c. As_2O_3
Total	440. gm.		

Crystals	100. gm.	96.09 p. c. KHCO_3	2.13 p. c. As_2O_3
Liquid	330. gm.	{ 2.0 p. c. KHCO_3 22.1 p. c. K_2CO_3	26.6 p. c. As_2O_3
Total	430. gm.		

III.) The results obtained so far lead to a desire for more information and the experiment was repeated on a still larger scale. In this case four times the original quantities were used. Instead of allowing the solution to stand over night it was cooled and the crystals formed at definite temperatures were removed and examined. The first crop of crystals was collected at 30°C ., the second crop at 20°C . Then the solution was placed out doors and allowed to stand over night. The next morning the liquid in the flask registered -10°C . A separation between the crystals and the liquid was effected as quickly as possible. At room temperature the separated crystals were apparently decomposing hence were placed in a funnel and allowed to stand twenty-four hours. By that time the crystals had lost approximately one-half of their bulk with the formation of a liquid. Each lot of crystals, likewise the

liquid resulting from the decomposition of the last lot was assayed. The following results were obtained:—

30° crystals	105 gm.	96.09 p. c. KHCO_3	1.73 p. c. As_2O_3
20° crystals	65 gm.	94.09 p. c. KHCO_3	1.24 p. c. As_2O_3
—10° crystals	96.09 p. c. KHCO_3	0.07 p. c. As_2O_3
liquid	{ 2.00 p. c. KHCO_3 15.2 p. c. K_2CO_3	12.3 p. c. As_2O_3

After the removal of the crystals at —10° C. the mother liquor was again placed out doors. Twenty-four hours later a second lot of crystals was removed, the temperature of the liquid being the same. These like the former decomposed at room temperature. The assay results are as follows:—

—10°C Crystals	97.09 p. c. KHCO_3	1.62 p. c. As_2O_3
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IV.) One gram of arsenic trioxide may be expected to react with 1.01, 2.02 and 3.04 grams respectively of potassium acid carbonate to form arsenites. The ratio of arsenic trioxide to potassium bicarbonate in the experiments I, II, and III, was 1 to 2. According to this there would be an excess of bicarbonate in the first combination, and this excess might be represented by the crystals that had been obtained. Hence the equivalent amount of pure⁹² potassium carbonate was substituted for the bicarbonate and the experiment repeated on the quarter kilo basis. The solution was allowed to stand over night, the crystals removed and assayed in the usual manner. The following results were obtained:—

Crystals	35.0 gm.	96.09 p. c. KHCO_3	1.5 p. c. As_2O_3
Liquid	430.6 gm.	28.00 p. c. K_2CO_3	22.5 p. c. As_2O_3
Total	465.00 gm.		

The mother liquor after standing in an open beaker for several days deposited a second lot of crystals⁹³ which assayed:—

Crystals	10 gm.	89.1 p. c. KHCO_3	2.9 p. c. As_2O_3
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⁹² Pure potassium bicarbonate was heated over a Bunsen flame to a constant weight. The resulting residue assayed 99.8 p. c. K_2CO_3 .

⁹³ In this lot the crystals were much larger and more of a cubical form. When powdered before assaying, a very moist powder resulted.

The presence of the potassium bicarbonate crystals would seem to indicate that a reaction had taken place between the arsenic trioxide and the potassium carbonate, and that the liberated carbon dioxide combined with some of the carbonate to form the bicarbonate.

V.) One hundred and twelve grams of potassium hydroxide, the equivalent of 200 grams of potassium bicarbonate, were dissolved in 100 mls of water and to the boiling solution 100 grams of arsenic trioxide were added. Then the mixture was immersed in a bath of boiling water until a clear solution resulted. After standing several days a solid mass⁸⁴ separated out. This was assayed with the following results:—

Weight 105.0, gm.	36.0 p. c. KOH	43 p. c. As_2O_3
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The mother liquor was allowed to stand at room temperature in an open dish and several portions of a similar mass were collected at various intervals. These were assayed with the following results:—

Second mass	36.5 p. c. KOH	43.0 p. c. As_2O_3
Third mass	19.6 p. c. KOH	21.67 p. c. As_2O_3
Fourth mass	19.07 p. c. KOH	19.9 p. c. As_2O_3

VI.) Fowler's solution is alkaline to litmus⁸⁵ due to the hydrolysis of the potassium arsenite.⁸⁶ In order to ascertain the alkalinity of the finished product three solutions were prepared of different composition. The first was prepared by dissolving 10 grams of arsenic trioxide and 20 grams of potassium bicarbonate in sufficient water to make 1000 grams; the second, 10 grams of potassium bicarbonate in 1000 grams of solution and the third by substituting an equivalent amount of potassium hydroxide for the bicarbonate of the first solution. These solutions were assayed for As_2O_3 and KHCO_3 with the following results:—

⁸⁴ The mass could not be removed from the beaker without breaking the dish so it was dissolved in water. Upon adding the water to this mass a lowering of temperature was noticed while solution was taking place, differing decidedly from the action of potassium hydroxide.

⁸⁵ United States Pharmacopoeia.

⁸⁶ *Kommentar zum Deutschen Arzneibuch*, 5. Ausgabe 1910.

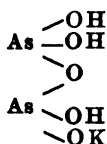
No. 1	1.01 p. c. As_2O_3	2.0 p. c. KHCO_3
No. 2	1.01 p. c. As_2O_3	1.0 p. c. KHCO_3
No. 3	1.09 p. c. As_2O_3	1.9 p. c. KHCO_3 (computed)

As the results obtained agree with the amounts used, within the limit of error,* one of two conclusions may be offered: viz. that no reaction takes place between the two compounds; or that the hydrolysis goes on during the titration until all of the arsenite is decomposed into acid and hydroxide.

VII.) The results obtained from the assay of Fowler's solution lead to the examination of some potassium arsenite of the market. A sample of Merck's pure potassium arsenite was assayed with the following results:—

<i>Found</i>			<i>Computed for $\text{KAsO}_2 + \text{H}_2\text{AsO}_3$</i>		
As_2O_3	65. p. c. equiv.	49. p. c. As.	72.75 p. c.	55. p. c. As.	
KOH	45. p. c. equiv.	31. p. c. K.	20.58 p. c.	14.3 p. c. K.	
H_2O		6.62 p. c.		

According to Merck's Report this salt has the composition $\text{KAsO}_2 + \text{H}_2\text{AsO}_3$. Structurally it may be represented by:—



VIII.) For a better understanding of the analytical data, the details of the method employed may be desirable:—

Ten grams of crystals or liquid were dissolved in water to make 100 mls. The alkalinity of these solutions, in ten mil titrations, was determined, first with phenolphthalein, and secondly with methyl orange. From the number of mls of N/1 acid required with each indicator the amounts of K_2CO_3 and KHCO_3 were com-

* Ten mls instead of ten grams were assayed. Hence the results are not exactly on a percentage basis.

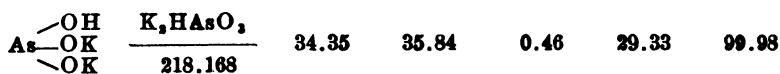
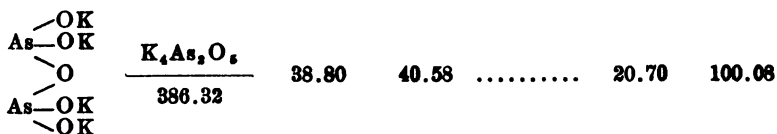
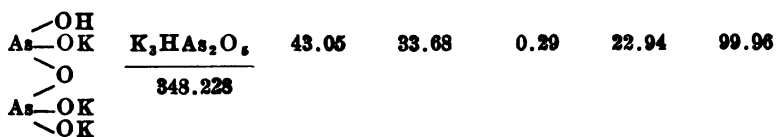
puted. To the titrated portions some sodium bicarbonate was added and the amount of As_2O_3 determined by titrating with N/10 iodine, using starch T. S. as an indicator. The computations were based on the following reactions:—

- I. $\text{K}_2\text{CO}_3 + \text{HOH} = \text{KOH} + \text{KHCO}_3$ } Phenolphthalein.
 II. $2 \text{KOH} + \text{H}_2\text{SO}_4 = \text{K}_2\text{SO}_4 + \text{H}_2\text{O}$ }
 III. $2 \text{KHCO}_3 + \text{H}_2\text{SO}_4 = \text{K}_2\text{SO}_4 + 2 \text{H}_2\text{O} + 2 \text{CO}_2$ Methyl orange.

Titration with phenolphthalein as an indicator gives one half of the carbonate. Then adding methyl orange, the remaining half of the carbonate (as bicarbonate) and any bicarbonate originally present is determined. Hence the quantity of acid consumed by the original bicarbonate is represented by the total used with methyl orange as the indicator (after neutrality has been reached with phenolphthalein), minus that used with the first indicator.

The following table reveals the computed percentage of the several components of possible arsenites.

	As.	K.	H.	O.	Total.	
$\begin{array}{c} \text{OH} \\ \diagup \\ \text{As} - \text{OH} \\ \diagdown \\ \text{O} \\ \diagup \\ \text{As} - \text{OH} \\ \diagdown \\ \text{OK} \end{array}$	$\frac{\text{KH}_2\text{As}_2\text{O}_6}{272.044}$	55.10	14.37	1.11	29.40	99.98
$\begin{array}{c} \text{As} = \text{O} \\ \diagdown \\ \text{O} \\ \diagup \\ \text{As} - \text{OH} \\ \diagdown \\ \text{OK} \end{array}$	$\frac{\text{KHAS}_2\text{O}_6}{254.028}$	59.01	15.39	0.39	25.19	99.98
$\begin{array}{c} \text{OH} \\ \diagup \\ \text{As} - \text{OH} \\ \diagdown \\ \text{O} \\ \diagup \\ \text{As} - \text{OK} \\ \diagdown \\ \text{OK} \end{array}$	$\frac{\text{K}_2\text{H}_2\text{As}_2\text{O}_6}{310.136}$	48.34	25.21	0.65	25.78	99.98



X.) For the sake of a more ready comparison with the theoretical computations of the previous tables, the results of the experiments from I to V are herewith tabulated:—

	N/I H ₂ SO ₄ with:—							N/10 iodine		
	phenolphthalein			methyl orange				starch T. S.		
	mils	D. C. K	D. C. K ₂ CO ₃	mils	D. C. K	D. C. KHCO ₃	D. C. K total	mils	D. C. As	D. C. As ₂ O ₃
I. crystals.....										
liquor.....										
II. crystals.....	0.0			9.6	37.5	96.00	37.5	3.4	1.27	1.7
liquor.....	1.6	6.25	22.1	1.9	1.07	3.02	7.32	40.2	15.06	19.9
crystals.....	0.0			9.4	36.8	94.00	36.8	4.3	1.61	2.13
liquor.....	1.6	6.25	22.1	1.3	0.78	2.0	7.03	53.9	20.0	26.6
III. 1st lot										
30° C. crystals.....	0.0			9.6	37.5	96.00	37.5	3.5	1.31	1.73
20° C. crystals.....	0.0			9.4	36.8	94.00	36.8	2.5	0.94	1.24
-10° C. { crystals....	0.0			9.6	37.5	96.00	37.5	1.4	0.52	0.70
{ liquid.....	1.1	4.3	15.2	1.3	0.78	2.0	5.03	24.3	9.3	12.3
2nd lot										
-10° C. { crystals....	0.0			9.7	37.9	97.00	37.9	3.25	1.22	1.62
{ liquid.....										
IV. crystals.....	0.0			9.6	37.5	96.00	37.5	3.0	1.12	1.5
liquor.....	2.03	8.90	23.0	0.0			8.00	45.4	17.0	22.5
2nd. crystals.....	0.0			8.9	34.8	89.1	34.8	7.7	2.9	3.8
3rd. crystals.....	0.0			9.77	38.2	97.7	38.2	2.65	0.90	1.31
4th. crystals.....	1.42	11.1	19.6	4.57	13.8	45.7	33.4	53.9	20.2	26.96

The results obtained from experiment V, viz. $\text{KOH} + \text{As}_2\text{O}_3$, are herewith tabulated. It must be remembered that no definite crystals were obtained in this experiment but a noncrystalline mass.

N/1 Acid.

N/10 Iodine.

	Phenolphthalein			Starch T. S.		
	mils	equiv. K	equiv. KOH	mils	equiv.	As equiv. As_2O_3
First mass. . .	6.4 cc.	24.0 p. c.	36.0 p. c.	86.8 cc.	32.5 p. c.	43.0 p. c.
Second mass .	6.5 "	25.4 "	36.5 "	85.2 "	31.9 "	42.2 "
Third mass ..	3.5 "	13.6 "	19.6 "	43.8 "	16.3 "	21.67 "
Fourth mass.	3.3 "	12.8 "	19.07 "	40.3 "	15.1 "	19.9 "

11.) *Compound Tincture of Lavender*. Fowler's original formula contains "a half ounce"⁹⁹ of Compound Spirit of Lavender. Of this addition he says⁹⁹ "The small Proportion of Compound Spirits of Lavender is added, merely for the sake of giving a medicinal appearance, least, from its being colorless and tasteless, those patients who may happen to be intrusted to drop it for themselves, should be tempted to use it with too great freedom; the consequences of which might frequently prove troublesome, if not sometimes dangerous." In this connection two things are noteworthy: firstly, that the Compound Spirit of Lavender contained the alcoholic extractive of cinnamon, nutmeg and red saunders¹⁰⁰ in addition to the aroma of the lavender, and secondly, that the patented preparation of Wilson,¹⁰¹ after which Fowler's preparation was modeled, contained red saunders as coloring matter though it contained no aromatic.

The London Pharmacopoeia of 1809, which apparently was the first to adopt Fowler's solution, likewise prescribed the use of Compound Spirit of Lavender. The authors of the U. S. P. of 1820, however, apparently regarded this addition or disguise as unnecessary or even undesirable. Thus Bigelow¹⁰² states that

⁹⁹ Fowler's Report, p. 79 (See Appendix).

¹⁰⁰ Ibidem, p. 82.

¹⁰¹ Pharmacopoea Collegii Regalis Medicorum Londinensis M. D. CCC. IX Editio altera. Lipsiae, 1816.

¹⁰² See description of patent in appendix.

¹⁰³ A treatise on Materia Medica intended as a sequel to the Pharmacopoeia of the U. S. (1832), p. 39.

"Pure alcohol is substituted instead of Compound Tincture of Lavender, which, from the variety of its ingredients may produce chemical changes." This is also true of the New York edition of 1830. Presumably, the alcohol addition was regarded as a preservative. The Philadelphia edition of 1830, however, came back to the original Compound Spirit of Lavender. This remained, until in 1880 when it was replaced by Compound Tincture of Lavender. This change is one of title only as the composition of the two was practically the same. The editors of the United States Dispensatory¹⁰⁸ state that "The spirit of lavender is added to give it taste, and prevent its being mistaken for water."

With the alkali of the arsenical solution the pigment of the red saunders possibly combines. (See No. 3:Preservation.)

The French Codex of 1818 uses spirit of melissa as flavoring agent, and adds no coloring matter, a precedent apparently followed by the German Pharmacopoeia up to this day.

12.) *The volume of the finished product.* According to Fowler's formula, the finished product was diluted to exactly one pint or, by weight, "fifteen ounces and a half." The U. S. P. in all its editions from 1820 to 1870 inclusive directs dilution to one pint. In the subsequent editions the ratio of arsenic trioxide to finished product is that of one part by weight to 100 parts by volume, whatever the amounts of the formula. The corresponding ratio of the earlier editions is 0.84 to 100.

The amounts and ratios of the London and British pharmacopoeias respectively are herewith tabulated:—

Pharmacopoeia.		As ₂ O ₃	K ₂ CO ₃	Vol. of product	Ratio
London.....	1809	64 gr.	64 gr.	1 pt.	} 0.84 to 100
"	1815	64 gr.	64 gr.	1 pt.	
"	1851	80 gr.	80 gr.	1 pt.	
British.....	1864	80 gr.	80 gr.	1 pt.	} 0.84 to 100
"	1885	87 gr.	87 gr.	1 pt.	
"	1898	87½ gr.	87½ gr.	1 pt.	
"	1898	10 gm.	10 gm.	1000 Cc.	} 1.00 to 100
"	1914	10 gm.	10 gm.	1000 Cc.	

¹⁰⁸ 13th edition, 1872, p. 1267.

It becomes apparent that the London Pharmacopoeia followed Fowler's formula and that when, in 1851, the Imperial pint of 20 fld. oz. was substituted for the wine pint of 16 fld. oz. the amounts of arsenic trioxide and potassium carbonate were increased accordingly leaving the percentage of arsenic trioxide the same. In 1885, however, the strength of the solution was made approximately that of one per cent. as had been done by the U. S. Pharmacopoeia of 1880 published in 1883. The more accurate approximation was made in 1898. With the abandonment of the old systems in 1914, the exact ratio of 1 to 100 was the simplest and hence the only natural one.

This does not imply, however, that the finished product contains 1 p. c. of arsenic trioxide or its chemical equivalent, for the *Arseni Trioxidum* of the U. S. P. and the Arsenous Anhydride of the B. P. are not necessarily 100 p. c. As_2O_3 . For further details on the percentage strength of the solution see No. 14.

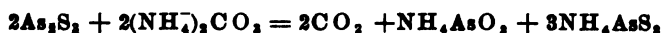
The "fifteen ounces and a half," the weight equivalent of Fowler's pint can be explained by calling attention to his statement in his original report (p. 80) in which he points out that the weights are expressed in Troy ounces and wt. avoirdupois "is always implied in the medical profession." According to the London Pharmacopoeia of 1836 (Phillips translation) the "wine" pint is equivalent to 7290 grains, and the Troy ounce contains 480 grains. Hence 7290 grains (the equivalent of the wine pint) are equal to 15.1 Troy ounces and not 15.5 ounces as stated by Fowler.

In 1837, Salles points out that whereas in those pharmacopoeias, in which the same system of weights and measures is used (Apothecaries weights and Wine measure) viz. "American of 1820, Antwerp of 1812, Batavia (Dutch) of 1805, Belgian of 1825, Edinburgh of (?), Hanover of 1823," etc. the strength of the finished product is the same, in the French Codex of 1818 it is different because the formula of the London Pharmacopoeia has been used "more or less literally" without taking into consideration the differences in weights and measures. Whereas the "oxide of arsenic" content of the London Pharmacopoeia is one-one hundred and twentieth. that of the French Codex is one-one hundredth. In order to correct this discrepancy, he suggests a formula, based on that of the London Pharmacopoeia (1:120) expressed in grammes or "parts by weight" so that it may be translated in any language and system without alteration of the strength of the finished product.

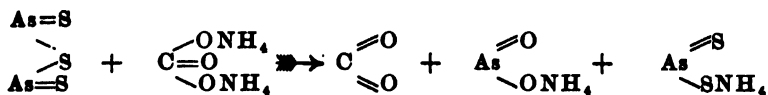
13.) *Appearance of the finished product.* The 1880 edition is the first edition of the U. S. P. that directs the finished product to be filtered after the reaction mixture has been allowed to stand eight days. Neinhaus¹⁰⁴ points out that this procedure was adopted to allow the formation of the precipitate that appears in Fowler's Solution and the subsequent removal by filtration.

14.) *Qualitative tests.* The last edition of the U. S. P., viz. that of 1910 is the only one that gives qualitative tests. Apparently these were regarded as necessary because of the enforcement of the Pure Food and Drugs Act of 1906. *The first paragraph* of these tests is descriptive. The faint opalescence of the solution is due to the oils¹⁰⁵ in the compound tincture of lavender; the pink color is that of the *Santalum Rubrum* also in the tincture. The alkalinity is due to the excess of potassium bicarbonate¹⁰⁵ used in the preparation, also to the hydrolysis of the potassium arsenite.¹⁰⁶

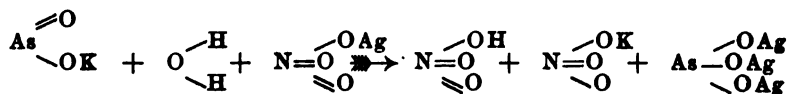
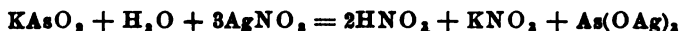
The second paragraph is an identity test for arsenic. Upon acidulating the solution with hydrochloric acid and saturating with hydrogen sulphide a yellow precipitate of arsenous sulphide is formed. This precipitate is soluble in Ammonium Carbonate T. S. The reaction with ammonium carbonate has been indicated as follows:¹⁰⁶



Structurally, the formulas involved may be represented in the following manner:



With Silver Nitrate T. S. the acidulated solution forms a yellow precipitate of silver arsenite. This has been expressed by the following equation:¹⁰⁶

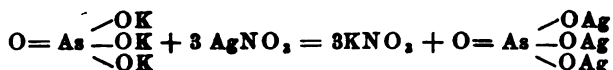


¹⁰⁴ Pharm. Ztg., 37, p. 331 (1892.)

¹⁰⁵ Commentar sur Pharmacopoeia Helvetica (1896), p. 196.

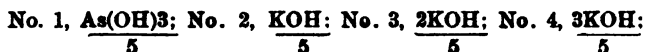
¹⁰⁶ Kommentar zum Deutschen Arzneibuch, vol. 2, p. 64. (1910.)

The third paragraph is a test for the absence or presence of arsenate. In the presence of hydrochloric acid the precipitate of silver arsenate does not form due to its solubility in the acid solution. If to the acidulated solution then, some Silver nitrate T. S. is added and a layer of ammonia water superimposed upon it a reddish brown color at the line of contact indicates the presence of silver arsenate. The reaction has been expressed in the following manner:¹⁰⁶



Supplement to Tests. According to the U. S. P. "An aqueous solution of Arsenic Trioxide is faintly acid to litmus." Whether this same acidity is shown towards other indicators is not stated. Hence a number of indicators were tested according to the following procedure:—

Aqueous solutions of arsenic trioxide and potassium hydroxide were prepared, their strength being represented by the following formulas:



respectively. Six test tubes of the same size were used for each series. Into these test tubes were placed the following solutions:—

Tube No. 1	5 mls of $\frac{\text{As}(\text{OH})_3}{5}$	+	5 mls of H_2O
Tube No. 2	5 mls of $\frac{\text{As}(\text{OH})_3}{5}$	+	5 mls of $\frac{\text{KOH}}{5}$
Tube No. 3	5 mls of $\frac{\text{As}(\text{OH})_3}{5}$	+	5 mls of $\frac{2\text{KOH}}{5}$
Tube No. 4	5 mls of $\frac{\text{As}(\text{OH})_3}{5}$	+	5 mls of $\frac{3\text{KOH}}{5}$
Tube No. 5	5 mls of $\frac{\text{KOH}}{5}$	+	5 mls of H_2O
Tube No. 6	10 mls of H_2O	

It will be noted that each solution as contained in the tubes was N/10 in strength, comparable in strength to the arsenical solutions.

The indicators used were of U. S. P. strength. Those not official were prepared according to a table given by Clark and Lub.¹⁰⁷ The following table represents the results obtained.¹⁰⁸

Indicator	p. c.	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
Cresol red04	acid—	alkaline	do.	do.	do. +	neutral
Phenol red04	acid—	alkaline	do.	do.	do.	neutral
Brasil wood	U. S.	acid	alkaline	do.	do.	do.	neutral
Litmus	U. S.	acid	alkaline	do.	do.	do.	neutral
Hematoxylin	U. S.	acid	alkaline	do. +	do. +	do. +	neutral
Brom-cresol—purple ..	.04	neut.	alkaline	do.	do.	do.	neutral
Brom-thymol—blue04	neut.	alkaline	do.	do.	do.	neutral
Rosolic acid	U. S.	neut.	alkaline	do.	do.	do.	neutral
Thymol blue04	neut.	alkaline	do.	do.	do.	neutral
Phenolphthalein... ..	1.0	"neut."	alkaline	do.	do.	do.	¹⁰⁹ neutral
Cochineal	U. S.	neut.	alkaline	do. +	do.	do.	neutral
Alkali blue	0.5	neut.	alkaline—	do. +	do. + +	do. +	neutral
Methyl red	0.2	neut.	alkaline	do.	do.	do.	neutral
Para-nitro-phenol	1.0	neut.	alkaline	do.	do.	do.	neutral
Congo red	0.5	neut.	alkaline	do.—	do.	do.	neutral
Turmeric.....	U. S.	neut.	alkaline	do.	do.	do	neutral
Methyl orange.....	0.1	no distinction in color of solutions					
Brom-phenol—blue... ..	0.4	no distinction in color of solutions					
Iodeosin	0.1	no distinction in color of solutions					
Eosin	0.1	no distinction in color of solutions					

A survey of the table reveals that only six out of twenty indicators show an acid reaction towards an aqueous solution of arsenic trioxide. Three of these viz. litmus, turmeric and hematoxylin are plant pigments, the composition of which is not well understood. The other three phenol red and cresol red are phenol-sulphone-phthalein, and ortho-cresol-sulphone-phthalein respectively, and phenolphthalein.

A peculiar change was noticed in the two series of solutions con-

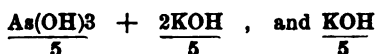
¹⁰⁷ Journal of Bacteriology, vol. 2, p. 1 (1917.)

¹⁰⁸ Tube No. 6 (H₂O) was taken as a standard, i. e. it was considered neutral, and any other tube showing same color was considered neutral.

¹⁰⁹ Phenolphthalein naturally does not reveal the acid reaction of the As₂O₃ solution.

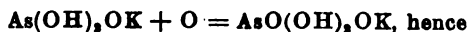
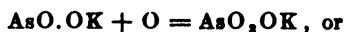
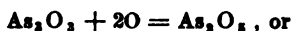
taining iodeosin and eosin, the former being tetra-iodo-fluorescein, and the latter a tetra-brom-fluorescein. Tubes 2, 3, and 4 of these series developed an intense yellow fluorescence when viewed by reflected light, which was not evident in the remaining tubes.

A third series worth mentioning is the one that contains alkali blue. In this series tubes 3 and 5 have the same color which differs from that of any of the remaining four. These tubes viz. 3 and 5, contained



respectively. Whether one may assume that one molecule of potassium hydroxide is uncombined in each tube, leaving one molecule combined with the $\text{As}(\text{OH})_3$ in the first tube is possibly open to question. Yet the sameness of color of these two tubes was so striking that the fact seemed worth mentioning.

15.) *Assay.* From 1880 on the U. S. P. gives directions for the assay of Fowler's Solution. The quantitative determination of trivalent arsenic as As_2O_3 is not only a check on the amount of arsenic trioxide employed, but also on the possible deterioration of the solution, brought about by the oxidation of the arsenite to arsenate, in the presence of water, as expressed by the following reactions:—



$$126.92 \text{ equiv. } \frac{197.92}{4}, \text{ or}$$

$$0.012692 \text{ equiv. } 0.004948$$

The amount of As_2O_3 as determined by the prescribed volumetric assay varies to a slight degree. The U. S. P. of 1880, the first to introduce an assay method, states that 24.7 gm. of the solution "should require from 48.5 to 50 cc. of volumetric solution of iodine"—("corresponding to 1 per cent. of arsenious acid of the required purity".) The As_2O_3 equivalents of 48.5 and 50 cc. respectively of N/10 I. V. S. are 0.9709 gm. and 1.001 gm. As the purity rubric for "arsenious acid" was "at least 97 per cent.

pure", ten grams, the amount directed to be used to make 1000 cc. of the Liquor, would represent 0.9700 gm. As_2O_3 to 100 cc. of the solution. Hence, unless the "arsenious acid" used assayed slightly higher than the minimum U. S. P. requirement, the finished product would fall short by a very slight amount (within the limits of experimental error) of the given standard.

The U. S. P. of 1890 states that 24.7 cc. of the solution "should require from 49.4 to 50. cc. of decinormal iodine V. S."—"(corresponding to 1 gm. of arsenous acid in 100 cc. of the solution)". The As_2O_3 equivalents of 49.4 cc. and 50. cc. N/10 I. V. S. according to this revision represent 0.9883 gm. and 1.004 gm. respectively of As_2O_3 in 100 cc. of the solution. As the purity rubric for "arsenous acid" in this revision is "at least 98.8 percent of arsenic trioxide", ten grams, the amount prescribed to make 1000 cc. of the Liquor, would represent 0.988 gm. to 100 cc. of the solution. In this case the minimum requirement would be met with.

The U. S. P. of 1900 states that 24.6 gm. of the solution "should require not less than 50 cc. of tenth-normal iodine V. S.—" "(corresponding to 1 gm. of arsenic trioxide in 100 gm. of the solution)". The As_2O_3 equivalent of 50 cc. N/100 I. V. S. according to this revision represents 0.9981 gm. of As_2O_3 in 100 gm. of the solution. The new purity rubric for arsenic trioxide is "not less than 99.8 per cent. of pure Arsenic Trioxide". Hence ten grams of arsenic trioxide, as directed to be used for the preparation of 1000 grams of the Liquor, would represent only 0.998 gm. of As_2O_3 to 100 gm. of the solution. In this instance the conditions meet the requirement of 10 gm. of arsenic trioxide, which represents 9.98 gm. of As_2O_3 .

The U. S. P. of 1910 merely demands a definite percentage strength, viz. "not less than 0.975 nor more than 1.025 gm. As_2O_3 in 100 gm. of the solution," and makes no mention of the amounts of N/10 I. V. S. to be used. The purity rubric for arsenic trioxide for this revision is "not less than 99.8 per cent. of As_2O_3 ." It is quite evident however, that the maximum limit of As_2O_3 content of the solution will probably not result when the prescribed ten grams of arsenic trioxide are used, as this represents only 0.998 gm. of As_2O_3 to 100 gm. of the solution. The lower limit of the rubric viz. 0.975 gm. to 100 gm. of solution, is undoubtedly to allow for a slight loss of arsenic trioxide, as determined by the assay process, due to the oxidation of the trivalent arsenic to the pentavalent arsenic.

Two factors influence the variations mentioned above: firstly, the variation in the As_2O_3 equivalent of N/10 I. V. S. due to changes in atomic weights, and secondly, the purity rubric of the arsenic trioxide. The Cc. equivalent for 1880 was 0.004945; for 1890, 0.004942; for 1900, 0.004911; and for 1910 it is 0.004948. The purity rubric for arsenic trioxide for 1880 was 97 p. c. As_2O_3 ; for 1890, 98.8 p. c. As_2O_3 ; for 1900, 99.8 p. c. As_2O_3 , and for 1910 it is 99.8 p. c. As_2O_3 .

In as much as only one gram of arsenic trioxide is used to prepare 100 grams of the solution, it becomes quite apparent that any solution assaying 1 p. c. As_2O_3 , (the generally accepted U. S. P. requirement) would result only from carelessness in weighing, unless it be that the U. S. P. formula were ignored and the equivalent of 10 gm. of 100 p. c. pure arsenic trioxide were used, or that a 100 p. c. arsenic trioxide were used.

16.) *Dose.* The 1900 revision of the U. S. P. is the first one to include the dose. This is given as "average dose—0.2 C. (3 minims)". The 1910 revision likewise contains the dose given as "average dose—Metric, 0.2 mils—Apothecaries, 3 minims".

"Doses were introduced into the Pharmacopoeia to meet a popular demand—mainly to add to the value of the book to the young physician, but also to serve as an authoritative statement for the benefit of the dispenser, of the ordinary practice of the physicians in prescribing different remedies".¹¹⁰ The subject of the introduction of doses into the Pharmacopoeia evidently called forth some little discussion, as to whether a maximum, a minimum, or an average dose should be designated. The objection to establishing a definite dose was the possibility of legal difficulties if this dose were overprescribed.¹¹¹ In reviewing the method in vogue for designating doses in foreign pharmacopoeias, the question of overprescribing and thereby ignoring the standard has apparently been overlooked, or considered unimportant. Or the revisors of the pharmacopoeias had not unlimited confidence in the prescribers knowledge of drugs and medicines, as to place no restrictions whatsoever on the quantity he may prescribe, for out of ten of the more recent revisions of foreign pharmacopoeias consulted, seven give a maximum dose. Three give no dose, but state that the solution must be dispensed with caution (or its equivalent). Not only is

¹¹⁰ Lyons, Cir. of the Comm. of Revision of U. S. P. VIII, Cir. 447, p. 1934.

¹¹¹ Remington, Ibidem, Cir. 447, p. 1821.

the maximum single dose given, but the maximum amount to be given "per diem" is prescribed. "Overprescribing the maximum amount in most of the European countries is indicated by having the physician place an exclamation mark (!) after such a prescribed dose. This reveals to the pharmacist that the prescriber wants the effect of something more than the 'average' maximum dose; this cautions him in his dispensing, and relieves him of the responsibility of 'too large a dose'.¹¹²"

The following table gives the dose of the European pharmacopoeias consulted:

Dose

1910 German.....	max. single, 0.5 g.	max. daily, 1.5 g.
1909 Italian.....	max. single, 0.5	max. daily, 1.5
1905 Holland.....	max. single, 500 mg.	max. daily, 1.5 gm.
1907 Switzerland.....	max. single, 0.5	max. daily, 1.5
1913 Norwegian.....	max. single, 0.5 gm.	max. daily, 2.0 gm.
1905 Spanish.....	max. single, 0.6	
1914 British.....	max. single, 0.5 centimils.	
1910 U. S.....	average 0.2 mils	
1906 Belgian.....	no dose given,	
1908 French.....	no dose given,	
1908 Swedish....	no dose given,	

¹¹² Kremers, *Ibidem*, Cir. 500, p. 2043.

APPENDIX

English Patents. (Patent Medicines.) "In the early days of English commerce, monopolies were granted by the sovereigns at their own pleasure, and often for their personal profit. Queen Elizabeth so largely abused her power in this direction that towards the end of her reign the discontent of her subjects compelled her to promise she would offend no more: and her successor, James I, gave a similar undertaking. The abuse, however, was continued until the Statute of Monopolies, passed in 1624, regulated all such grants, placing the power in the hands of Parliament, and limiting the period of privilege to fourteen years.

For the first century or thereabouts of the administration of this Act, specifications of processes or formulas were not a condition of the patent. The idea was the introduction into the country of new industries, and it was supposed that artificers who would have to be employed in any such industries would certainly acquire such necessary skill and knowledge about any new manufacture as would prevent any perpetuation of the monopoly. It was during the reign of Queen Anne that the law officers began to require that specifications should be filed before letters patent were issued. But the condition was not by any means uniformly or intelligently insisted upon, as will be seen immediately in the case of certain patent medicines.

The term 'patent medicines' as now popularly used, means generally secret medicines, and the meaning is therefore in exact contradiction to the expression. Truthfully to declare the composition of many of these proprietary compounds would ruin their sale. Not that the ingredients are often improper or injurious; this rarely occurs; but because the success of these remedies in most instances is rather on the mystery with which the maker can surround them than on their exceptional merit.

But some old medicines which became popular, including a few the reputation of which lives today, were actually patented. The first compound medicine for which a patent was granted under the Act of 1624 was No. 388, and was dated October 22, 1711. It was granted to Timothy Byfield for his *sal oleosum volatile*, 'which

by abundant experience hath been found very helpful and beneficial as well in uses medicinal as others.' No particulars of the ingredients or method of manufacture are given." (Wootton, *Chronicles of Pharmacy*, Vol. II, pp. 161-2.)

* * *

MEDICAL COMPOUND.

Wilson's Specification.

To all to Whom these presents shall come, I, Thomas Wilson, of Snow Hill, in the Parish of Saint Sepulchre's, in the City of London, Chymist, send greeting.

Whereas His most Excellent Majesty King George the Third, by his Letters Patent under the Great Seal of Great Britain, bearing date at Westminister, the Sixteenth day of February, in the twenty-first year of his reign, did give and grant unto me, the said Thomas Wilson, His especial licence that I, the said Thomas Wilson, during the term of years therein expressed, should and lawfully might use, exercise, and vend, within England, Wales, and Town of Berwick-upon-Tweed, my invention of "*A Medicinal Composition, which after much Experience hath been found to be an Infallible Remedy for Agues and Intermitting Fevers, even in the most obstinate Cases where the Bark and every other Medicine hath proven ineffectual*;" in which said Letters Patent there is contained a proviso obliging me, the said Thomas Wilson, under my hand and seal, to cause a particular description of the nature of the said Invention to be inrolled in His Majesty's High Court of Chancery within four calendar months after date of the said recited Letters Patent, as in and by the same (relation being thereunto had) may more fully and at large appear.

Now Knowe Ye, that in compliance with the said proviso, I, the said Thomas Wilson, do hereby declare that my said Invention of a Medical Composition, which, after much Experience hath been found to be an Infallible Remedy for Agues and Intermitting Fevers, is described in the Manner following, (that is to say):—

Take of centarium minus, or common centaury, any quantity, burn it to ashes; take of these ashes, boil them in water for three hours, evaporate the liquid to dryness; take this mass, calcine it for four or five hours, keeping it constantly stirring. Take cob-

balt,¹¹³ powder it fine, put it in a crucible; sublime the flowers; take these flowers, add to the above, melt them together and boil them for two hours in water; then take of the santalum rubrum, or red sanders, boil it in water for four hours; mix all together.

In witness whereof, I, the said Thomas Wilson, have hereunto set my hand and seal, this Eleventh day of June, 1781.

Thomas Wilson. (L. S.)

And Be it Remembered, that on the same Eleventh day of June, in the year above mentioned, the aforesaid Thomas Wilson came before our said Lord the King in His Chancery and acknowledged the Specification aforesaid, and all and every thing therein contained and specified, in form above written. And also the Specification aforesaid was stampt according to the tenor of the Statute made in the sixth year of the reign of the Late King and Queen, William and Mary of England, and so forth.

Inrolled the same day and year above mentioned.

* * *

MEDICAL REPORTS OF THE EFFECTS OF ARSENIC IN THE CURE OF AGUES, REMITTING FEVERS, AND PERIODIC HEADACHES.

by

Thomas Fowler M. D.

Physician to the General Infirmary of the County of Stafford.

Together with a Letter from Dr. Arnold, of Leicester, and Another from

Dr. Withering, describing their Experience of the Effects

of Arsenic in the Cure of Intermittents.

London, MDCCL XXXVI.

(Title page of report.)

PREFACE. p. ii.

¹¹³ "This kind of pyrites miners call *oobaltum*, if it is allowed to me to use our German name. The Greek call it *cadmia*. The juices, however, out of which pyrites and silver are formed, appear to sliffy into one body, and thus is produced what they call *oobaltum*. There are some who consider this the same as pyrites, because it is almost the same. There are some who distinguish it as species, which please me, for it has the distinctive property of being extremely corrosive, so that it consumes the hands and feet of the workmen, unless they are well protected, which I do not believe that pyrites can do." (Bermannus, p. 459.) Hoover's Engl. transl. of Agricola, *De re metallica*, p. 113. Hoover adds: "It is desirable to bear in mind that the mines familiar to Agricola abounded in complex mixtures of cobalt, nickel, arsenic, bismuth, zinc, and antimony. Agricola frequently mentions the garlic odour from *cadmia metallica* which, together with the corrosive qualities mentioned below (above) would obviously be due to arsenic."

The Medical Reports, which the Author lately published, relative to the Effects of Tobacco, in the Cure of Dropsies and Dysuries, having been favourably received by the Public; and the general diuretic Property of that Medicine, confirmed by further Experience; he is encouraged to pursue the same Plan, with Regard to another powerful Article of the *Materia Medica*.

Arsenic is a Mineral which has long been reputed one of the most violent Poisons hitherto known; and accordingly has been reprobated in the strongest Terms by almost every medical Writer, that has ever deigned to notice it; and yet there is a good Reason to believe it (p. III) bids fair to hold a Place, among the best and most valuable Medicines; and to rank with peruvian Bark in the Cure of Agues, remitting Fevers, and periodic Headachs.

Efficacious Medicines are certainly of the utmost Importance in Practice, the Investigation of which, has been frequently recommended by many celebrated Philosophers and Physicians, who have done Honour to Science amongst the Ancients; and by some Authors of the highest Reputation amongst the Moderns, particularly Bacon, Boyle, Baglivi, and Boerhaave. The present *Materia Medica*, however, notwithstanding the many Volumes that have been written upon the Subject, makes but a very humble Appearance with Regard to Medicines of real Efficiency and Importance; and therefore, if by an experimental Enquiry, another efficacious Medicine is likely to be added to the Number of the few valuable Ones already established, it is to be hoped, that such an Attempt will not be deemed unworthy of Attention.

(p. IV.) Perhaps by some it may be alleged, that the Ague is a very common and insignificant Disease, because frequently cured both by Art and Nature, and that consequently there is no Occasion for the Investigation of a new Medicine on that Account. But certainly it is a Disease of much Importance; for whenever it continues long, Coldness, Paleness, and Debility are its constant Concomitants, and evince it to be the fertile Parent of Cachexy; and when it occurs in old Age, or in Constitutions broken down by Intemperance, or some previous Disease, how often do we find it accelerate the Accession of Jaundice, Consumption, Dropsy, or some other Mischief of fatal Consequence.

(p. V.) Fatal however as the Disease has been in its Consequences, it is well known to practitioners that there are many Cases wherein not only the minor Remedies have proved ineffectual, but

even the Bark itself has failed, or otherwise its Administration not been admissible; and therefore a powerful vacarious Remedy for so frequent a Distemper, becomes an important Object.

(p. VI) It may also be objected, that to introduce a Poison to the Public as a general Medicine, is to put a two-edged Sword into the Hands of the Ignorant. But the same Argument will equally apply against several of the most efficacious Medicines in daily Use, in particular Opium, and some of the more active preparations of Mercury and Antimony.

Or if for a Moment, the Force of this Argument be admitted, yet when it is considered that a Patent Medicine has, for some years past, been largely circulated through the Kingdom, as a specific for Agues, under the Title of Tasteless Ague and Fever Drops; that from its Effects in Practice there is the strongest Reason to believe it to be an arsenical preparation; and that on this very Ground, it is at present imitated in different Parts of the Kingdom, the Objection becomes nugatory.

Therefore, if any new and important Medicine, either from its active Nature, or an imprudent Administration thereof, is found to be sometimes connected with distressing and deleterious Effects, it becomes highly requisite (p. VII) that the Public should speedily be made acquainted with such Effects, as far as they are known; together with such Precepts, Cautions, and Restrictions, as may tend to unite the greatest Degree of Safety with its Efficacy. Nothing however, of this Sort, has been done; which Consideration, it is presumed, will be an Apology for an early Publication of so interesting a Subject, and for such Imperfections as may have taken Place from that Circumstance.

When the Patent Ague Drops began to acquire some Reputation in the Country, they were occasionally adopted in the Hospital Practice of this Place, in 1781, 1782, and 1783, and were found efficacious.

In the beginning of October 1783, Mr. Hughes, the Apothecary to the Infirmary, (whose Industry, Attention and Abilities in his professional Line, justly merit Applause) informed the Author that he had tried to imitate the Ague Drops, and, from a number of Experiments, had so far succeeded (his Medicine having produced similar Effects) that he was convinced they were a Preparation of Arsenic.

(p. VIII) In Consequence of this general Intimation the Author

of these Sheets consulted Lewis's *Materia Medica* upon arsenic,¹¹⁴ and agreeable to his pharmaceutic History of that Article, he dissolved a small Portion of the white Sort in a solution of fixed vegetable Alkali.¹¹⁵ On trying and comparing the Effects of this Solution, with those of the Patent Ague Drops, he found the Medicine to be similar, but the former was too strong; he therefore diluted the Solution, by doubling the Proportion of Water, and then comparing their Effects, found the Medicines nearly of an equal Strength.

Having thus become acquainted with what he esteemed a powerful Medicine, he was strongly impressed with an Idea of its Importance; and therefore has kept a regular and connected History of the Cases in which he has prescribed it. Hence the following Reports contain an Account of the curative Effects of the Medicine, described in a just Proportion of Examples of Successes and Failure, in the Course of its Administration. They also contain a particular (p. IX) Account of its operative Effects, which being sometimes troublesome, both in Degree and Number, will be found to merit a serious Attention. They are likewise divided into Sections, in order that Cases of similar Nature, Treatment or Event; and also the Observations more immediately appertaining to each particular Part of the Subject, might appear in a more clear and practical Point of View.

The cases drawn out at large are but few, and those which are abstracted are not so numerous as Some might think necessary, considering the Number which the Writer has collected. But certainly it is sufficient for an Author, to deliver, in as concise a manner as possible, such a View of the Result of his Experiments, with the Mode of conducting them, as may be clearly understood and readily applied to Practice. Beyond this Point, a Multiplicity of Cases and Arguments is of no Consequence; because every Publication which appeals to the Reality of Facts for its Importance, will soon have its Propositions either confirmed or rejected, by the daily Experience of the Public.

(p. X) The Author professes himself a strong Advocate for an effective and powerful *Materia Medica*; on which Account, the Subjects of his late and present Reports have engaged a Share of his

¹¹⁴ For complete title see p. 148.

¹¹⁵ Of "white arsenic" Lewis (*Mat. Med.*, p. 101) states that it is "soluble plentifully in alkaline lixivis." See also statement in Wilson's patent on p. 188.

most serious Attention. The Properties however of mild and simple Medicines, have occasionally been the Objects of his Investigation; and his Enquiries in that Line have convinced him, that among the many trifling and insignificant Articles, which are still retained in the *Materia Medica*, there are some valuable Medicines, that are not in the Reputation they are justly entitled to; a few Examples of which, it will give him Pleasure to communicate in some future Publication. In the meantime, as the Idea of a Poison seems to be so strongly connected with that of Arsenic, it will be found very difficult to separate them in the Mind, whenever that Term is named; and therefore to avoid as much as possible, such a disagreeable Association of Ideas, in the Practice of the healing Art, the Medicine now about to be introduced to the Notice of the Public, will be distinguished by the Name of *Mineral Solution*.

ADVERTISEMENT. (p. XI)

All Cases beginning with the Words In-Patient, and Out-Patient, belong to the Infirmary; the Rest were chiefly such as the Author gave Advice to at his own House.

When the Mineral Solution is ordered thrice a Day, six o'clock in the Morning, two in the Afternoon, and ten o'clock in the Evening; and when twice a Day, ten in the Morning, and ten in the Evening, are to be considered as the medicinal Hours, or Periods for its Administration.

Unless the Solution be ordered in some particular Vehicle it is always to be understood, that Adults are to take in a Tea cupful of Water, and the Doses for Children are to be given in the same Vehicle, proportionately diminished.

Every Medicine prescribed by a general title, without a Reference, is to be found in the London Dispensatory.

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Sect. III. (pp. 62-64)	Cases of Agues, suspended, relieved and not relieved, by the Mineral Solution, from the irregular Attendance of Patients, with Observations.

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- Sect. VII.** Observations on the Doses and Mode of administering the Mineral Solution, in the Cure of Agues, interspersed with Practical Rules and Cautions.
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 (pp. 108-116)

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Formulae Medicamentorum :
 with Observations.

Solutio Mineralis. (No. 1.)

Recipe Arsenici albi in Pulverem substillissimum triti;

Salis alkalini fixi vegetabilis purificati; singulorum Grana
Sexaginto quatuor,

Aquae fontanae distillatae Libram dimidiam.

Immittantur in Ampullam florentinum, qua in Balneo Arenae
posita, Aqua lente ebulliat, donec Arsenicum perfecte solutum
 fuerit. Deinde Solutioni frigidae adde

Spiritus Lavendulae compositi

Unciam dimidiam,

Aquae fontanae distillatae Libram dimidiam, plus vel minus, adeo
 (p. 80) **ut Solutionis mensura Libra una accurate. fit, vel potius**
Pondere* quindecim cum dimidia.

* I have said, *vel potius Pondere*, because weight is a much more accurate Method of ascertaining Proportions than Measure, in preparing Medicines of great Activity, of which Sort the Mineral Solution is a strong Example. It is perhaps superfluous to remind the Reader, that Troy Weight (which differs materially from Avoirdupois) is always implied in medicinal Professions.

Observations p. 81.

The first medicine is a chemical Preparation as simple as could be wished for, and if proper Care be taken that the Solution of the Mineral is complete, it will be found of a certain and uniform Degree of Strength. Its being also (p. 82) in a liquid Form, renders it convenient, for administration by Drops, and thereby nicely varying the Doses, according to the Exigencies of the Case; a matter of some Importance, where the Activity of the Medicine is so great.

The small Proportion of Compound Spirits of Lavender is added, merely for the Sake of giving a medicinal Appearance, lest, from its being colourless and tasteless, those Patients who may happen to be intrusted to drop it for themselves, should be tempted to use it with too great Freedom; the Consequences of which might frequently prove troublesome, if not sometimes dangerous.

To a Pint of the Solution, sixty-four Grains were added, for the purpose of a more ready Calculation; therefore one Ounce of the Solution contains exactly four Grains of the Mineral and consequently each Dram, just half a Grain; I have found by repeated Trials of dropping the Solution, from a two Ounce Vial (with a broad Margin) little more than half full, that each Dram, by a two Ounce graduated Glass Measure, contains about eighty Drops.

We ought to be well assured, that the fixed vegetable Alkali we make Use of is perfectly pure; for that which is bought of the Druggists is frequently so impure, as to be inadequate for the Purpose of producing a perfect Solution of the Mineral; a Circumstance which would occasion great Confusion and Uncertainty, in the Doses (p. 83) of the Medicine, if therefore any One desirous of preparing the Mineral Solution, should not be provided with the pure alkali; and would not choose to be at the Trouble of purifying it, a double Proportion of purified Nitre (which is a preparation of some certainty, and supposed to be always at Hand), may be substituted; for the Arsenic having the Property of discharging the nitrous acid, will unite with the Alkali.

The Formula which I have given with the Alkali, contains my own preparation, alluded to in the Preface, and is that on which my experience is chiefly founded.

Mr. Hughes has likewise used it prepared with Nitre, and on trial found it equally efficacious. I have also used it a Number of

Times, and found it successful, and believe the two Solutions to be the same Medicine, provided they are accurately prepared with either of the purified Salts.

A Letter from Dr. Arnold, Physician to the General Infirmary, and to the Dispensary, at Leicester. (p. 117).

Dear Sir:

I was pleased to learn, by your last, that your intended publication relative to the cure of intermittents by means of an arsenical Preparation, is in such forwardness; and shall willingly contribute my assistance, to establish the credit of a remedy of which I am led by experience to form a very favourable opinion. With this in view you at length receive a short sketch of my observations, on the use of Arsenic in the cure of intermittents; which I flatter myself will be found to correspond in a great measure with your own, and those of our friend, *Doctor Withering*; who first communicated to me the uses of this new Medicine, and the method of preparing it.

I would most readily have sent you a complete summary of my practice in this respect; in which I would have left it to facts to speak for themselves; but am obliged to decline an undertaking, which would require more time than is compatible with your haste, and my present leisure.

(p. 118) The medicine I have made use of is a solution of the common *arsenicum album* of the shops; of which the following is the formula. Recipe Arsenici albi pulveris subtilissimi grana octo,

Aquae distillatae uncies octo.

Digire in balneo mariae donec penitus solvatur arsenicum. Caveas autem ne aquae vel guttula evaporetur; quae non statim, solutioni finita, reponatur. Per chartam deinde cola.

Dosis a guttulis quindecim ad quadraginta, ter in die, inter februm intermittentium paroxysmos, in menthae vulgaris infusi uncies duabus.

(Note) The remainder of the letter refers to the dosage, symptoms and diagnosis, of cases observed).

(Signed) (p. 123) Your faithful friend and fervent,

THOMAS ARNOLD.

West-Cotes

March 27th, 1786.

A Letter from W. Withering. M. D. F. R. S. (p. 123)

Birmingham, May 21st. 1786.

Dear Sir:

The Arsenical Solution was first used here in the Autumn of the year 1783, at which time Intermittents of various denominations were very prevalent both in this and in adjoining Counties. The general use of *Tasteless Ague and Fever Drops* of this period made me solicitous to know the composition of that medicine, and I was informed it was made from the Ore of Cobalt; but as it did not answer the usual tests for that Semi-

metal, I thought it was probably Arsenic, which is known to abound very generally in cobalt Ores.* Whilst I was intending to submit the drops to a more (p. 124) effectual examination, my good friend and your excellent Apothecary Mr. Hughes informed me, that he had made an analysis of the drops, and found them to be a solution of Arsenic.

At first we gave the medicine cautiously,.... (This part of the letter deals with the dose and treatment of patients)..... In the Autumn of 1784 it was almost constantly prescribed, and has ever since maintained its credit with us under a very great number of trials.

At first we used a simple solution of *Arsenicum album*, one grain to each Ounce of distilled Water. The solution is facilitated by boiling for a minute to two in a Florence Flask, or other glass Vessel, but long continued boiling disposes it to precipitate again. After some time Mr. Baley (p. 125) added Nitre to the solution, by the direction of Mr. Hughes, to prevent the precipitation, which in the rapid consumption in the Hospital had hardly been observed to take place, but in the smaller demands of private practice seldom fails to happen. I should also mention that an ounce of alcohol has lately been added to twenty Ounces of the Solution, but I am doubtful of the propriety of this addition.

(The remainder of the letter deals with the dose and method of administration)

(Signed) (p. 127) Your obliged and faithful friend

W. WITHERING.

* See footnote to Thomas Wilson's patent, p. 49 for chemical explanation.

CARDS

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- 6.) Liquor Potassii Arsenitis, U. S. P. 1890
- 7.) Linogen
- 8.) Linoliment
- 9.) Linoval
- 10.) Parogen(um)
- 11.) Penetrole
- 12.) Petrogen
- 13.) Petrolatum Saponatum
- 14.) Petroliment
- 15.) Petroxolin(um)
- 16.) Valselol
- 17.) Valsol
- 18.) Vasapon
- 19.) Vascosan
- 20.) Vaselon
- 21.) Vaseloxyne
- 22.) Vasenol
- 23.) Vasogen(um)
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- 25.) Vasoliment(um)
- 26.) Vasopotent(um)
- 27.) Vasoval
- 28.) Liquor Potassae Arseniatis, U. S. P. 1820
- 29.) Liquor Arsenicalis, U. S. P. 1830 (N. Y.)
- 30.) Liquor Potassae Arsenitis, U. S. P. 1830 (Phila.)
- 31.) Liquor Potassae Arsenitis, U. S. P. 1840
- 32.) Liquor Potassae Arsenitis, U. S. P. 1850
- 33.) Liquor Potassae Arsenitis, U. S. P. 1860
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- 42.) Ludwig, H.:—Geschichte der Apotheker
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